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Evidence Summary FA-4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Focal Tumour Ablation 4: Early-stage Primary Lung Cancer and Lung Metastases

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Focal Tumour Ablation 4: Early-stage Primary Lung Cancer and Lung Metastase

Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated Programs is editorially independent from the OMHLTC.

INTRODUCTION

Lung cancer is the leading cause of death in Canada, even though there has been a substantial reduction in the lung cancer death rate, particularly for men, over the past 25 years. Lung cancer is one of the most common cancers, with one in 12 men, and one in 15 women expected to be diagnosed with it in their life time; it represents 14% of all new cases diagnosed in men and women [1].

Traditionally, early-stage lung cancer has been treated with lobectomy with systematic mediastinal node evaluation. More recently, non-surgical treatment options have become available, including percutaneous ablative therapy (radiofrequency ablation [RFA], cryoablation [CRYO] and microwave ablation [MWA]) as well as stereotactic body radiotherapy (SBRT). These minimally invasive management strategies are best suited to patient populations that are not suitable candidates for surgery.

As opposed to primary lung cancer discussed above, secondary lung cancers or lung metastases represent spread of cancer from a malignant origin outside of the lungs. Surgical resection of lung metastases or pulmonary metastasectomy, performed when the primary tumour is controlled and no extrathoracic lesions are present, is believed to be effective in improving patient survival based on registry data and surgical follow-up studies [2]. Patients with colorectal cancer or sarcoma commonly develop lung metastases and may be considered for pulmonary metastatectomy; percutaneous ablative therapy is an option for those who are not surgical candidates.

In Ontario, practice is variable in regard to these new strategies, and the Interventional Oncology Steering Committee decided to conduct this evidence report, in collaboration with the CCO PEBC to provide an evidentiary base to its six-part Focal Tumour Ablation Recommendations Report 2015. (Summary available at www.cancercare.on.ca/fta).

RESEARCH QUESTIONS

These research questions were developed to direct the search for available evidence on focal tumour ablation for early-stage primary lung cancer and lung metastases:

1. **What is the effectiveness of focal tumour ablation for the treatment of patients with early-stage primary lung cancer or lung metastases?**
2. **What are the complications associated with focal tumour ablation for early-stage primary lung cancer or lung metastases?**
3. **What patient populations are most likely to benefit from focal tumour ablation for early-stage primary lung cancer or lung metastases?**

TARGET POPULATION

Patients with early-stage, primary lung cancer or lung metastases.

INTENDED PURPOSE

To provide a systematic literature review that will be one of the six components of the Recommendation Report of the Interventional Oncology Steering Committee (other components will include demand forecasting, costing analysis, jurisdictional review, system capacity, literature review, and current state, summary available at https://www.cancercareontario.ca/en/cancer-care-ontario/programs/clinical-services/specialized-services-oversight/focal-tumour-ablation?redirect=true.)

INTENDED USERS

Clinicians (radiologists, thoracic surgeons, medical and radiation oncologists, and respirologists) involved in the delivery of focal tumour ablation for lung cancer patients.

METHODS

This evidence summary was developed by the Focal Tumour Ablation Working Group consisting of interventional radiologists, diagnostic radiologists, surgical oncologists, and a health research methodologist at the request of the Interventional Oncology Steering Committee. The Working Group was responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix 1.

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

This project was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/).

Search for Existing Systematic Reviews

A literature search was performed using MEDLINE, EMBASE (Ovid interface) for systematic reviews published as systematic reviews or as part of guidelines with publication date from 2008 to October 5, 2015, and the Cochrane Library (to Issue 9, 2015), first and then for primary studies. The search strategies and key words used are reported in Appendix 2 A) and B). The citations of the primary studies referenced by the retrieved systematic reviews were also pulled and added to the primary studies retrieved from the database searches.

Additionally, the following resources were checked for systematic reviews, practice guidelines, or relevant primary studies:

The Inventory of Cancer Guidelines (SAGE): http://www.cancerview.ca/sage, the National Guideline Clearing House: http://www.guideline.gov/, the Canadian Medical

Association Infobase: https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx, and International Guideline Developers such as National Institute for Health and Clinical Excellence (NICE; UK): http://www.nice.org.uk/guidance, the Scottish Intercollegiate Guidelines Network (SIGN; UK): http://www.sign.ac.uk/guidelines/index.html, American Society of Clinical Oncology (ASCO; US): http://jco.ascopubs.org/site/misc/specialarticles.xhtml, PROSPERO: http://www.crd.york.ac.uk/PROSPERO/, and the National Health and Medical Research Council (Australia): http://www.nhmrc.gov.au/guidelines/search?subject=30695.

Evidence was selected and reviewed by the methodologist (FB) and independently audited. The final document was independently reviewed by the other authors (JK, SA, MM, and RM).

Search for Primary Studies

The search for primary studies covers areas that were not discussed by existing systematic reviews (e.g., time periods, adverse events, or topics that the existing systematic reviews did not discuss). Therefore, the criteria for inclusion and exclusion for primary literature were specified after these gaps were known.

Study Selection, Data Extraction and Analysis

Literature Search Strategy

The literature search strategies for primary studies of CRYO, MWA, and RFA are reported in Appendix 2B.

Study Selection Criteria and Process

The criteria used to select primary studies are reported in Appendix 3. Early-stage lung cancer is defined as tumours that are ≤3 cm in diameter that have not extended into the membranes that surround the lungs (pleura), and that have not spread into the lymph nodes (N0) or distant organs (M0).

The methodologist (FB) reviewed the titles and abstracts of citations to identify potentially relevant articles, which were then retrieved in the library for full-text review. For items that warranted full-text review, the methodologist and three of the Working Group members (JK, RM, and SA) reviewed the publications and discussed the results during a meeting.

Data Extraction and Assessment of Study Quality and Potential for Bias

The methodologist (FB) extracted data and summarized the characteristics and summary results into tables. All extracted data were audited by an independent auditor.

The methodologist (FB) evaluated included reviews with "A Measurement Tool to Assess Systematic Reviews" (AMSTAR) instrument [3]. Identified systematic reviews were evaluated based on their clinical content and relevance. The results of the AMSTAR and clinical assessment were used to determine whether any existing systematic review could be incorporated as part of the evidentiary base.

Quality of comparative observational studies was evaluated with the Cochrane ACROBAT-NRSI tool [4]. This tool assesses the bias of comparative nonrandomized studies in relation to an ideal randomized trial, and covers seven domains through which bias can be introduced in a nonrandomized trial: 1) bias due to confounding; 2) bias in selection of participants into the study; 3) bias in measurement of interventions; 4) bias due to departures from intended interventions; 5) bias due to missing data; 6) bias in measurement of outcomes; and 7) bias in selection of the reported results. In the application of this tool it is required that the authors, at the protocol stage, identify, among the seven domains of bias, those that are expected to be more relevant to all or most studies. At the protocol stage, the authors should

also identify the possible co-interventions that could have an impact on study outcomes. A second part of the tool requires the evaluation of each included study by answering specific questions.

The observational, non-comparative studies were considered to be of low quality and no further quality assessment was made.

Synthesizing the Evidence

The Working Group members did not expect to find any randomized controlled trials, and expected to find clinically heterogeneous interventions, populations, and outcomes in the identified observational comparative studies; therefore, statistical pooling of the results was not planned.

RESULTS

Search for Existing Systematic Reviews

We reviewed 131 citations at the title and abstract level, and 34 articles were selected and reviewed at the full-text level. A total of 12 systematic reviews were included: six formed the evidentiary base of existing guidelines [5-10], and six were stand-alone systematic reviews [11-17] (Table 1). Reasons for exclusion at full text are reported in the study flow chart (Appendix 4 A).

Table 1 shows the general characteristics, and Table 2 presents the AMSTAR assessments of included systematic reviews.

Four of the included guidelines were large documents on the general management of pulmonary cancer, and they included a brief section on focal tumour ablation techniques [5,7,8,10]. Because their main focus was not on focal ablation, they will be considered only for discussion purposes.

The Working Group decided that the reviews by Chan et al. [17], Kennedy et al. [12], Lee et al. [16] and the 2013 report by the National Institute for Health and Clinical Excellence [6] will form the evidence base for the interventions of interest (i.e., RFA, CRYO, and MWA). These reviews were chosen because of their higher quality and because their questions were the most similar to the research questions of the present study. The remaining four systematic reviews [9,11,14,15] were used as a source of evidence. The evidence generated by the systematic reviews was integrated with a search for primary studies. Table 3 presents, question by question, the source of evidence that was used for this report (i.e., existing systematic reviews versus primary literature), what years were covered with the search, and where a meta-analysis was available.

Table 1. Focal tumour ablation of lung cancer and lung metastases: General characteristics of included systematic reviews

Author, date, funding source,	Search cut-off date	Review objectives/ Design	Study Number and design included	Population	Intervention, comparison(s)	Outcomes
Guidelines						
Callister, 2015 [5] **Funding:** British Thoracic Society	June 2014	**Objectives**: To provide a summary and a reference text for the management of pulmonary nodules **Design:** Guideline on general management of lung cancer based on a systematic review, guideline recommendations according to AGREE	**Study number**: RFA (n=25 studies); microwave ablation (n=2); percutaneous cryotherapy (n=1). **Design**: case series and poor-quality retrospective cohort studies.	Studies including pts with presumed or pathologically proved malignancy	RFA	OS, AE
NICE, 2013** [6] **Funding:** Healthcare Improvement Scotland	July 2013	**Objectives:** To help members of the NHS Interventional Procedures Advisory Committee make recommendations about the safety and efficacy of microwave ablation **Design:** Guideline based on a rapid review and specialist opinion	**Study number:** 10 **Design:** 7 retrospective case series, and 3 case reports	Studies including pts with primary or metastatic lung cancer	MWA	OS, DFS, TTP, local recurrence rate, distant recurrence rate, retreatment, AE
Donington, 2012 [7] **Funding:** American College of Chest Physicians	Feb 2010	**Objectives**: To produce recommendations to assist clinicians in the evaluation and treatment of high-risk patients with stage 1 NSCLC **Design**: Guideline on general management of lung cancer based on a systematic review	**Study number:** 8 **Design:** case series	Studies including pts with high-risk stage I NSCLC	RFA	CSS, OS
Howington, 2013 [8] **Funding:** American College of Chest Physicians	End of 2011	**Objectives:** To provide guidelines on the diagnosis and treatment of early stage (I and II) NSCLC (update previous recommendations) **Design:** Guideline on the general management of lung cancer based on a systematic review and recommendations	**Study number:** 6 **Design:** *nr* Note: this is based on the review by Donington [7]; therefore, it does not have its own review	Studies including pts with NSCLC	RFA	Tumour control, OS, CSS, AE

Author, date, funding source,	Search cut-off date	Review objectives/ Design	Study Number and design included	Population	Intervention, comparison(s)	Outcomes
NICE, 2010** [9] Funding: National Institute for Health and Clinical Excellence	Mar 2010	**Objectives:** To help members of the NHS Interventional Procedures Advisory Committee make recommendations about the safety and efficacy of radiofrequency ablation **Design:** Guideline based on a rapid review and specialist opinion	**Study number and Design:** 9 case series 6 case reports 1 systematic review 789 pts with primary or lung cancer metastases (NSCLC and SCLC) in 7 series and 5 reports, and 493 procedures in one series (pts number nr) and 1584 pts included in the systematic review	Studies including pts with lung cancer	Percutaneous RFA	Safety and efficacy outcomes (OS, local control, PFS, symptom palliation), quality of life, AE and deaths
Lim, 2010 [10] **Funding**: British Thoracic Society	Not reported	**Objectives:** To update the 2001 guidelines for the selection and assessment of patients with lung cancer for radical treatment **Design:** Guideline on the general management of lung cancer based on a systematic review (SIGN methodology)	**Study number:** *nr* **Design:** *nr*	Studies including pts with stage I NSCLC lung cancer	RFA	Survival, toxicity
Systematic reviews						
Schlijper, 2014 [11] **Funding**: Not reported	Oct 2011	**Objectives:** To compare the outcome of surgery, RFA and SBRT specifically in the treatment of lung metastases of colorectal cancer **Design:** Systematic review	**Study number:** 27 4 RFA (retrospective), and 23 surgical (4 prospective and 19 retrospective) **Design:** case series	Studies including pts with metastases from colorectal cancer	RFA, SBRT, and surgery	Local control AE
Kennedy, 2014 [12,13] **Funding**: NRreported	Feb 2014	**Objectives:** To assess potential risk factors for pneumothorax after RFA **Design:** Systematic review and meta-analysis	**Study number:** 10 (represented by 12 publications) **Design:** case series, retrospective, single group	Studies including pts with primary or metastatic disease	RFA	Prevalence of pneumothorax Factors that are predictors of pneumothorax
Renaud, 2013 [14] **Funding**: Not reported	2012	**Objectives:** To compare RFA with SBRT in patients with a primary lung cancer **Design:** Systematic review	**Study number:** 5 (RFA), 17 (SBRT) **Design:** cohort studies: prospective (3 RFA) and retrospective (2 RFA); prospective (10 SBRT), retrospective (6 SBRT), and 1 meta-analysis (SBRT)	Studies including pts with NSCLC not candidates for surgery	RFA, and SBRT	Procedure efficiency, Mortality, Morbidity, Toxicity, Survival rate Local recurrence

Author, date, funding source,	Search cut-off date	Review objectives/ Design	Study Number and design included	Population	Intervention, comparison(s)	Outcomes
Carrafiello, 2012 [15] **Funding:** Not reported	Nov 2010	**Objectives:** To review AE of RFA and MWA **Design:** Methods of systematic review *nr*	**Study number:** 14 RFA 2 MWA (2 animal studies) **Design:** *nr*	*Nr*	RFA and MWA	Major AE (%) Minor AE (%)
Lee, 2011 [16] **Funding:** Ministry for Health, Welfare and Family Affairs	2008 (month not available)	**Objectives:** To investigate safety and efficacy of endoscopic CRYO of endobronchial tumours **Design:** Systematic review (SIGN methods)	**Study number:** 16 **Design:** case studies (15), and comparative observational (1)	Studies including pts with lung or bronchial tumours	CRYO using bronchoscopy compared to: laser therapy, electrocauterization, brachytherapy, stent insertion, and photodynamic therapy	Safety (deaths and AE at 30 ds) Response rate Improvement in performance and quality of life
Chan, 2011 [17] **Funding:** Not reported	Jun 2009	**Objectives:** To assess percutaneous RFA **Design:** Systematic review and case series	1 review of 26 studies (observational) and 46 primary studies (case series with >5 pts)	Studies including inoperable pts with NSCLC and operable pts with pulmonary metastases	Pts with primary NSCLC: pRFA versus beam RT; Pts with pulmonary metastases: pRFA vs.surgery	Local recurrence, survival rate, safety outcomes

*Includes pain, pneumothorax, and pleural effusions.
**NICE produced an interventional guidance document also for cryotherapy in lung cancer, it is dated 2005, so it was not captured by our search.
***The surgical series provided 2-year SR range from 64–88%. The 5-year SR reported for surgery ranged from 29–71.2%.

Abbreviations: AE = adverse events; CRYO = cryoablation; CSS = cancer-specific survival; DFS = disease-free survival; ds = days; hrs = hours; MWA = microwave ablation; NHS = National Health Service (England); *nr* = not reported; NSCLC = nonsmall cell lung cancer; OR = odds ratio; OS = overall survival; PFS = progression-free survival; pRFA = percutaneous radiofrequency ablation; Pts = patients; QOL = quality of life; RFA = radiofrequency ablation; RT = radiotherapy; SBRT = stereotactic radiotherapy; SCLC = small-cell lung cancer; SIGN = Scottish Intercollegiate Guidelines Network; TTP = time-to-progression; yrs =years.

Table 2. AMSTAR assessment of included systematic reviews of focal tumour ablation for primary lung cancer and metastases

Author, year, [ref]	Focal ablation modality and population	An *a priori* design provided	Duplicate study selection and data extraction	Comprehensive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
	Systematic reviews from guideline publications											
Callister, 2015 [5]	Management strategies (among which RFA, MWA, and CRYO) in pts with pulmonary nodules	**Y**[a]	**Y**	**Y**	**N**	**Y**[b]	**N**	**N**	**Y**	**Y**	**N**	**Y**
NICE, 2013 [6]	MWA in pts with primary lung cancer and metastases	**Y**	**N**	**N**	**N**	**Y**[b]	**Y**	**Y**[c]	**N**	**Y**	**N**	**N**
Howington, 2013 [8]	Management strategies (among which RFA) in pts with Stage I and II NSCLC	**Y**[a]	**N**	**Y**	**N**	**Y**[b]	**Y**	**N**	**N**	**N**	**N**	**N**
Donington, 2012 [7]	Management strategies (among which RFA) in pts with Stage I NSCLC	**N**[a]	**N**	**N**	**N**	**Y**[b]	**Y**	**N**	**N**	**N**[d]	**N**	**Y**
NICE, 2010 [9]	RFA in pts with primary lung cancer and metastases	**Y**	**N**	**N**	**N**	**Y**[b]	**Y**	**Y**[c]	**N**	**Y**	**N**	**N**
Lim, 2010 [10]	Management strategies (among which RFA) in pts with lung cancer	**Y**[a]	**N**	**Y**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**Y**
	Systematic reviews publications											
Schlijper, 2014 [11]	RFA, surgery, and SBRT for pts with lung metastases from colorectal cancer	**Y**	**N**[e]	**Y**	**N**	**Y**[b]	**Y**	**N**	**N**	**Y**	**N**	**Y**
Kennedy, 2014 [12,13]	Risk factors for pneumothorax in pts undergoing RFA for lung cancer	**Y**	**Y**	**Y**	**Y**	**Y**[b]	**Y**	**Y**	**N**	**Y**	**N**	**Y**

Author, year, [ref]	Focal ablation modality and population	An *a priori* design provided	Duplicate study selection and data extraction	Comprehensive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Renaud, 2013 [14]	RFA or SBRT for pts with primary NSCLC unsuitable for surgery	**Y**	**N**	**Y**	**N**	**Y**[b]	**Y**	**N**	**N**	**N**	**N**	**Y**
Carrafiello, 2012 [15]	AE of RFA and MWA in pts with lung lesions	**Y**[f]	**N**	**N**	**N**	**Y**[b]	**N**	**N**	**N**	**Y**	**N**	**Y**
Lee, 2011 [16]	Endoscopic CRYO in pts with lung and bronchial tumours	**Y**	**N**	**Y**	**Y**	**Y**[b]	**Y**	**N**	**N**	**Y**	**N**	**Y**
Chan, 2011 [17]	RFA for patients with primary or metastatic lung cancer	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**N**	**N**	**N**

[a] The aim of this guideline was to provide comprehensive guidance on the management of lung cancer. Focal ablation is a small portion of the guidance document.
[b] No references of excluded studies are provided.
[c] Quality characteristics of included studies are provided under the heading 'comments' in the tables.
[d] This study was a consensus guideline, which used some standard search strategies.
[e] Study selection was done by one author; each included study was examined by two authors.
[f] This publication present a primary institutional study and a systematic review, but it is primarily a primary study publication

Abbreviations: AE = adverse events; CRYO = cryoablation; MWA = microwave ablation; NSCLC = nonsmall cell lung cancer; RFA = radiofrequency ablation; SBRT = stereotactic radiotherapy.

Table 3. Sources of evidence for each research question and each intervention modality.

Research Questions	Systematic Review Used	Primary Studies Identified
RFA		
1. What is the effectiveness of focal tumour ablation for the treatment of patients with early-stage primary lung cancer or lung metastases?	Chan et al. 2011 [17] **Years searched:** From inception to Jun 2009 **Design:** systematic review, without meta-analysis; included noncomparative observational studies	**Design:** 6 comparative observational studies and 1 abs publication: *Pts with primary lung cancer:* 5 studies [18-22]; *Pts with lung metastases:* 1 abs publication [23]; *Pts with lung cancer and metastases:* 1 study [24] **Years searched:** from 2009 to Dec 2015
2. What are the complications associated with focal tumour ablation for early-stage primary lung cancer or lung metastases?	Chan et al. 2011 [17] (see characteristics above) Kennedy et al. 2014 [12] **Years searched:** from inception to Feb 2014 **Design:** systematic review and meta-analysis of studies of patients who experienced pneumothorax after RFA for a lung tumour. Included single arm studies.	**Design:** 3 comparative non-randomized studies, and 1 abs: *Pts with primary lung cancer:* 2 studies [18,22] *Pts with lung metastases:* 1 abs [23] *Pts with lung cancer and metastases:*1 study [24] **Years searched:** Search for adverse events other than pneumothorax from 2009 to Dec 2015
3. What patient populations are most likely to benefit from focal tumour ablation for early-stage primary lung cancer or lung metastases?	Chan et al. 2011 [17] **Years searched:** From inception to Jun 2009 **Design:** systematic review, without meta-analysis. Included noncomparative observational studies	**Design:** 3 comparative non-randomized studies, and 1 abs: *Pts with primary lung cancer:* 3 studies [18,21] [22], and 1 abs publication [20] *Pts with lung metastases:* no studies identified *Pts with lung cancer and metastases:* no studies identified **Years searched:** from 2009 to Dec 2015
Cryoablation		
1. What is the effectiveness of focal tumour ablation for the treatment of patients with early-stage primary lung cancer or lung metastases?	Lee et al. 2011 [16] **Years searched:** from inception to 2008 **Design:** systematic review limited to endoscopic cryotherapy of endobronchial tumours, without meta-analysis. The included studies were noncontrolled.	No comparative studies were identified. **Years searched:** from 2009 to Dec 2015
2. What are the complications associated with focal tumour ablation for early-stage primary lung cancer or lung metastases?		
3. What patient populations are most likely to benefit from focal tumour ablation for early-stage primary lung cancer or lung metastases?		
Microwave ablation		
1. What is the effectiveness of focal tumour ablation for the treatment of patients with early-stage primary lung cancer or lung metastases?	NICE [6] **Years searched:** 2008 to 2013 **Design:** rapid systematic review without meta-analysis. Included studies were noncomparative.	No comparative studies were identified. **Years searched:** from 2013 to Dec 2015
2. What are the complications associated with focal tumour ablation for early-stage primary lung cancer or lung metastases?		
3. What patient populations are most likely to benefit from focal tumour ablation for early-stage primary lung cancer or lung metastases?		

Abs = abstract; NICE = National Institute for Health and Clinical Excellence; Pts = patients; RFA = radiorequency ablation

Search for Primary Literature

Fifty-five primary studies were included after full-text review. The study flow chart in Appendix 4B reports all the details of study selection and the reason for exclusion at full text. We report below the results for each intervention.

Radiofrequency ablation (RFA)

Seven comparative studies were included: four full publications [18,19,21,22] and a conference abstract [20] had a population of patients with primary lung cancer; an abstract publication included patients with lung metastases [23]; and one included patients with primary lung cancer or lung metastases [24]. All had a cohort design, except for Matsui et al. [24], which was a case control study and compared patients who experienced phrenic nerve injury following RFA with patients who did not. Two studies used the Surveillance, Epidemiology and End Results (SEER) registry linked to MEDICARE data [20,21], while the others used institutional data.

At the protocol stage, the domains of bias that were anticipated to be common to most nonrandomized trials were bias due to confounding, and bias due to selection of patients. The anticipated co-interventions were patients in one group may have received adjuvant chemo- or radiotherapy, while patients in the other group may have not.

Other domains of bias encountered in this body of evidence were bias in measurement of interventions, since RFA was often conducted using different systems and protocols; bias due to departures from intended interventions, since most often information about possible co-interventions such as additional adjuvant treatment was not reported; and bias in measurement of outcomes, since outcome assessors blinding was never reported.

Evaluation of the quality of the five fully published comparative studies with the Cochrane ACROBAT-NRSI tool showed that the risk of bias was critical in three studies [18,19,24], serious in one study [22], and moderate in one study [21].

Tables 4a and 4b present the general characteristics and summary results of comparative studies, and Table 4c presents the summary quality assessment of the studies that were fully published. Appendix 5 reports the quality assessment conducted with the Cochrane ACROBAT-NRSI tool [4] in detail.

Thirty-one studies of RFA were noncomparative [25-55]. Five of these studies were abstract publications [26,28,47,53,54] and will not be discussed any further. These noncomparative studies are not discussed any further except for adverse events outcomes. Their general characteristics and summary results are reported in Tables 1a and 1b in Appendix 6; quality was not measured for these studies.

Outcomes: **RFA**

Question 1: "What is the effectiveness of RFA for the treatment of patients with early-stage primary lung cancer or lung metastases?"

The systematic review by Chan et al. [17] identified a previous systematic review of 26 observational studies, and 46 observational noncomparative studies, published from 2006 to 2009. The authors documented an evolving trend over time of changing techniques for RFA: sedation over time changed from general anesthesia to conscious sedation, needles from single-tip to multi-tined electrodes, follow-up from computed tomography (CT) to a combined approach using CT and positron emission tomography, and, in more recent years, smaller rather than larger tumours were chosen for treatment with RFA.

Local recurrence was reported in 24 of 46 included studies; time to local recurrence ranged from three to 45 months, and recurrences ranged from 0% to 65%. The included studies reported a range of follow-up ranging from one to 77 months. Overall survival (OS) was reported

in 21 of 46 studies and ranged from 25% to 100%; cancer-specific survival (CSS) (24 of 46 studies) ranged from 58% to 100% in studies of patients with primary disease (8 studies) and from 55% to 90% in study patients with metastatic disease (10 studies).

Unlike the previous systematic review, our systematic review included comparative, although nonrandomized, studies only. The results are summarized in the following paragraphs, and in more detail in Table 4b.

Survival

Patients with primary lung cancer

OS: Four fully published studies compared RFA with surgery, and showed that, when adjusting for tumour and patients' characteristics, RFA and surgery resulted in a similar OS [19,21], while when confounders were not controlled for [18,22] surgery was better than RFA (see numerical results in Table 4b).

CSS: Three fully published studies reported on CSS [21,22,30]. CSS was consistently better in patients treated with surgery than in those treated with RFA, whether confounders were controlled for or not. (see Table 4b for numerical results).

Patients with metastatic disease

OS: The only available evidence for this population at this time was a recent abstract publication by Tselikas et al. [23]. The authors showed no statistically significant difference in OS between surgery and RFA (Table 4b).

Disease control

Patients with primary lung cancer

Progression-free survival (PFS): After controlling for age and tumour size, Safi et al. [19] did not show any difference between RFA and surgery.

Disease-free interval (DFI): Ambrogi et al. [18] found a statistically significant better DFI for surgical patients than for those treated with RFA at two, four, and five years (data not adjusted for confounders).

Time-to-recurrence (TTR): Alexander et al. [22] found that TTR was significantly longer in patients in the surgical group (see Table 4b for numerical results).

Patients with metastatic disease.

PFS: Tselikas et al. in a recent abstract publication [23] showed no statistically significant difference between surgery and RFA in PFS (Table 4b).

Recurrence

Patients with primary lung cancer and patients with metastatic disease

Local recurrence was significantly higher in patients who received RFA compared with various types of surgery in three studies, and this held true whether confounders were adjusted for or not [18,19,23] (Table 4b).

Distant, and regional recurrence were no different between groups as reported in two studies [18,19].

No data were reported on RFA re-treatment after recurrence (Table 4b).

Other outcomes

Patients with primary lung cancer and patients with metastatic disease

Length of hospital stay was significantly shorter for patients who received RFA than surgery [18,22,23].

Question 2: "What are the complications associated with RFA for early-stage primary lung cancer or lung metastases?"

Chan et al. [17], in their systematic review, identified pneumothorax, pain, and pleural effusions as the most prevalent side effects of RFA.

The systematic review and meta-analysis by Kennedy et al. [12] examined the risk factors for pneumothorax. This review included 10 retrospective cohort studies with 981 patients and 1916 RFA sessions. The prevalence of pneumothorax in this sample was 37% (95% confidence interval [CI], 29% to 46%). The risk factors for pneumothorax were older age (mean difference [MD] between patients with and without pneumothorax, 2.09; 95% CI, 0.11 to 4.06), male gender (unadjusted odds ratio [OR], 2.20; 95% CI, 1.49 to 3.27); no history of lung surgery (unadjusted OR, 0.29; 95% CI, 0.19 to 0.44); and a larger number of ablated tumours (MD, 0.50; 95% CI, 0.27 to 0.73).

Our systematic review of primary studies included three comparative studies that reported on adverse events. Alexander et al. [22] reported on major adverse events for RFA versus surgery, but did not provide any statistical tests results (gastrointestinal: 12.5% vs. 10.71%; respiratory: 32.14% vs. 17.86%; cardiac: 16.07% vs. 14.29%; and secondary therapy: 25% vs. 28.57%); Ambrogi et al.[18] reported a statistically significant difference in grade 2 adverse events for RFA compared with wedge resection (4% [three pneumothorax requiring chest tube] vs. 17% [five atrial fibrillation, two wound dehiscence, two anemia, one urinary retention], p=0.01); while Tselikas et al. in an abstract report of patients with metastatic disease [23] reported a nonstatistically significant difference in adverse events rates for RFA vs. surgery: 32% vs. 29%, p=0.8.

One among the comparative studies [24] examined the risk factors for specific adverse events of RFA: larger tumour size (≥20 mm; p=0.014), proximity of the phrenic nerve to the tumour (<10 mm; p<0.001), the use of larger electrodes (≥3 cm; p=0.001), and higher power applied (>100 W; p>0.001) were significantly associated with the development of phrenic nerve injury.

Gender, tumour, and ablation zone distance from the chest wall, and ablation zones involving visceral pleura were all significant risk factors for rib fracture [45]; puncture number, and previous chemotherapy were significant risk factors of aseptic pleural effusion; previous external beam radiotherapy and age were risk factors for pneumonia; serum platelet count and tumour size were risk factors for bleeding; and emphysema was a predictor of lung abscess and a risk factor for pneumothorax [49]. Lesions of small diameter, located in the basal and middle lung zones, possible injury to vessels during ablation, and the use of multi-timed electrodes were reported as risk factors for hemorrhage [50]. More than two lesions treated, and a longer probe trajectory were reported as risk factors for overall morbidity including pneumothorax, and need for a chest drain [55]. Numerical results are reported in Table 4b for the comparative studies and in Appendix 6, Table 1b for the non-comparative trials.

Question 3: "What patient populations are most likely to benefit from RFA for early-stage primary lung cancer or lung metastases?"

Patients with primary lung cancer:

Four of the included comparative studies presented data on patient subgroups [18,20-22].

Tumour stage: Patients with stage IA were shown to respond in the same way to RFA as to wedge resection for OS, CSS and DFI [18]; patients in stage 1B were shown to have a worse survival than patients in stage IA [21] (see numerical results in Table 4b). Similar results were reported, among the noncomparative studies, by Hiraki et al. [31] (Appendix 6, Table 1b).
Tumour size: In an abstract publication, Ezer et al. [20] showed no difference in OS and CSS between patients with tumours ≤3 cm in diameter treated with RFA or with radiotherapy (numerical results in Table 4b). Similar results were reported, among the noncomparative studies, by Dupuy et al. [25], Lanuti et al. [29], Hiraki et al. [31,51], Gillams et al. [36], Soga et al. [40], Yamakado et al. [41], and Garetto et al. [44], all showing that smaller tumours had better outcomes than larger tumours (Appendix 6, Table 1b).
Tumour histology: Patients with squamous cell carcinoma or not specified histologic type had higher hazard of death than patients with other tumour histologies [21] (Table 4b).
Age and gender: Older patients were shown to have worse survival, while females had lower risk of death [21] (Table 4b).

Patients with metastatic disease
No subgroup analyses were reported in the included comparative studies for patients with metastases.

Table 4a. Comparative studies of radiofrequency ablation: General characteristics.

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Control	Outcomes
Studies of Primary Lung Cancer					
Ambrogi, 2015 [18] **Country:** Italy **Funding:** NR	Retrospective cohort[a] **Data collection:** 2006 to 2012 **Follow-up:** **Ig**: 42 mos **Cg**: 36 mos	N=121 pts with stage I NSCLC T1/T2N0M0 who were marginal or nonsurgical candidates treated with curative intent. **Lesion size:** median (range) **Ig:** 23 mm (12–43 mm) **Cg**: 26 mm (12–33 mm) **Gender:** **Ig**: Men 73% **Cg**: Men 78% **Age:** median (range) **Ig:** 76 yrs (60–88 yrs) **Cg:** 70 yrs (56–83 yrs)[b]	RFA (n = 62) **Device:** a generator RITA-Model 1500/1500X (AngioDynamics, Latham, NY, US) with a 14-gauge needle cannula with 9 deployable electrodes that open flower-like up to 5 cm **Target temperature:** 90˚C maintained from 15 to 27 min, and 105˚C, maintained for 5 to 9 min. **Procedure:** Pts received conscious sedation and local anesthesia. **Operator experience**: NR	WR (n = 59)	OS CSS DFI LR FFR DR LOS
Safi, 2015 [19] **Country**: Germany **Funding**: NR	Cohort **Data collection:** Jan 2009 to Dec 2013 **Follow-up:** (median): SLR: 18 RFA: 13 RT: 10	N=116 pts with stage I NSCLC **Lesion size (mm), range:** SLR: 18.5±9.5, 2 to 45 RFA: 21.9±7.3, 10 to 35 RT: 28.4±9.8, 10 to 50 **Gender:** Men: SLR: 64% RFA: 72% RT: 69% **Age[cd]:** SLR: 69.6±7.1 yrs; range, 53 to 84 yrs RFA: 71.2±6.4 yrs; range, 55 to 80 yrs RT: 73.5±7.2 yrs; range, 57 to 89 yrs **ECOG:** 0: SLR: 43%; RFA: 16%; RT: 20%. 1: SLR: 57%; RFA: 84%; RT: 66%. 2: SLR: 0; RFA: 0; RT: 14%	RFA (n=25) **Device:** Bipolar RFA (Celon LABPower; single bipolar Celon® ProSurge RFA probe) single probe for tumours ≤2.0 cm, and multipolar RFA (Celon® LABPower; multiple bipolar Celon® ProSurge RFA probes) for tumours 2.0 to 3.0 cm. Monopolar RFA (Boston Scientific® RF 3000; LeVeen 3-cm RFA probe) for tumours >3 cm. **Target temperature:** **Procedure:** Pts received bipolar RFA under general anesthesia. The technique of RFA depended on the tumour size according to the manufacturer's recommendation. **Operator experience**: NR	SLR (n=42) RT (n=49)	OS PFS PR Locoregional recurrence Regional recurrence Distant recurrence AE
Ezer, 2014 [20] **ABS** **Country**: US **Funding**: Les Fonds de	Analysis of registry data **Data collection:** 2007 to 2009 **Follow-up:** NA	N=2015 pts with unresected stage I-II NSCLC **Lesion size:** NR **Gender:** NR **Age:** NR	RFA (n=37) **Device:** NR **Target temperature:** NR **Procedure:** NR **Operator experience**: NR	RT	OS CSS

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Control	Outcomes
Recherche en Santé du Québec					
Kwan, 2014 [21] **Country**: US **Funding**: Society of Interventional Radiology	Comparative non-randomized trial (using SEER-Medicare linked data) **Data collection:** Jan 2007 to Dec 2009 **Follow-up:** (mean) 508 ± 310 (SD) ds (16.7 mos)	N=1897 pts with early-stage lung cancer with stage IA or IB NSCLC **Lesion size:** NR **Gender:** Men 44.5% **Age:** 65-69 yrs 22.9%; 70-74 yrs 28.9%; 75-79 yrs 26.8%; >79 yrs 21.4%	RFA (76 pts) **Device:** NR **Target temperature:** NR **Procedure:** NR **Operator experience**: NR	SLR (96% of pts)	OS CSS Predictors of OS
Alexander, 2013b [22] **Country**: US **Funding**: NR	Cohort (retrospective) **Data collection:** Aug 2000 to Nov 2009 **Follow-up:** NR	N=84 pts with stage IA or IB **Lesion size:** NR **Gender:** Ig: Men 42.86% Cg: Men 42.86% **Age:** Ig: 77.6±6.6 (SD) yrs; Cg: 73.8±5.9 (SD) yrs;	RFA (n=56) **Device:** A generator and perfusion pump (Radionics CC-1; Valley Lab; Boulder, CO, US) and a coupled electrode were used. **Target temperature:** 60°C; if this temperature was not reached after the first application, the treatment was repeated for a max time of 12 min. **Procedure:** Pts received conscious sedation (i.v. midazolam and fentanyl) and local anesthesia with 1.5% lidocaine. **Operator experience**: 4 interventional radiologists with between 2-17 years of experience	Surgery (WR or segmentectomy (n=28)	OS CSS Time to recurrence LOS AE
Studies of Lung Metastases					
Tselikas, 2015 [23] **ABS** **Country**: France **Funding**: NR	Comparative observational **Data collection:** NR **Follow-up:** NR	N=204 pts with 130 lung metastases from extra-pulmonary cancer. **Lesion size:** ≤4 cm **Gender:** NR **Age:** NR	RFA (n=126) **Device:** NR **Target temperature:** NR **Procedure:** NR **Operator experience**: NR	Surgery (n=78)	OS PFS Local recurrence Pulmonary progression AE LOS
Studies of Primary Lung Cancer and Lung Metastases					
Matsui, 2012 [24] **Country**: Japan **Funding**: NR	Case-control **Data collection:** Jun 2001 to Dec 2011 **Follow-up:** NR	N=90 pts 786 RFA procedures **Lesion size:** Cases: 23.6±6.2 mm Controls: 18.7±13.7 mm **Gender:** Cases: Men 40% Controls: Men 68.75%	Cases of phrenic nerve injury **Device:** A generator (RF 2000 or RF 3000 [Boston Scientific] or CC-1 [Covidien]) with two types of electrodes: a multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA, US) or a single internally cooled electrode (Cool-tip; Covidien, Mansfield, MA, US).	Controls: no injury	Phrenic nerve injury incidence AE: phrenic nerve injury.

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Control	Outcomes
		Age: Cases: 64±9.7 yrs Controls: 61.3±10.8 yrs;	**Target temperature:** The energy was applied until a rapid increase in impedance or automatic shut off after 15 min, or, using an impedance control algorithm, for 10 to12 min, depending on the device used. **Procedure:** Pts received conscious sedation (im hydroxyzine 25 mg, and iv fentanyl 0.1 to 0.3 mg) plus local or local and epidural analgesia. **Operator experience**: NR		Risk factors for phrenic nerve injury

[a] Patients who were treated with RFA belonged to a previous prospective study and patients treated with wedge resection were retrospectively selected from the authors' surgical database.
[b] Patients in the RFA group had also higher comorbidity score (not reported in the table) and worse performance status because RFA was indicated for patients who had some surgical contraindication.
[c] Patients in the SLR group were significantly younger (SLR vs. RT: p=0.012; SLR vs. RFA: p=0.37) and had a significantly better ECOG status (SRL vs. RFA: P=0.024)
[d] RFA patients were older than those undergoing sublobar resection or SBRT (p=0.02).

ABS = abstract; AE = adverse events; Cg = control group; CSS = cancer-specific survival; DFI = disease-free interval; DR = distant recurrence; ds = days; FFR = freedom from recurrence; Ig = intervention group; im = intramuscular; iv = intravenous; LOS = length of hospital stay; LR = local recurrence; mos = months; N = sample size; NR = not reported; NSCLC = nonsmall cell lung cancer; OS = overall survival; PFS = progression-free survival; PR = primary tumour recurrence; Pts = patients; RFA = radiofrequency ablation; RT = radiotherapy; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute; SLR = sub-lobar resection; WR = wedge resection; yrs = years.

Table 4b. Comparative studies of radiofrequency ablation: Summary results

Author, year, (ref)	Intervention and comparison	OS, CSS, Mortality/morbidity	Disease control (e.g., PFS, DFI)	Recurrence	Risk factors, predictors of outcome	LOS and AE	Subgroups	Authors conclusions
Studies of Primary Lung Cancer								
Ambrogi, 2015 [18]	RFA vs. WR	**30 ds and 90 ds mortality:** 0 vs. 0 **OS rates*** At 1 yr: 93% vs. 100% At 2 yrs: 72% vs. 96% At 5 yrs: 35% vs. 52% p=0.044 **CSS rates***: At 1 yr: 100% vs. 100% At 2 yrs: 73% vs. 98% At 5 yrs: 59% vs. 68% p=0.024 **Morbidity:** 16% vs. 27% p=0.128	**DFI rates:** At 1 yr: 87% vs. 96% At 2 yrs: 63% vs. 90% At 5 yrs: 55% vs. 76% p=0.01	**LR rates**: 23% vs. 2%, p=0.002. **DR rates:** 11% vs. 12%, P=NS **FFR** rates: 71% vs. 86%, p=0.01.	FEV_1 predicted: NS	**LOS:** Mean (range): 2 ds, (1 to 4 ds) vs. 6 ds (4 to 22 ds) P<0.001 **AE:** Grade 1: 13% vs. 10% p=0.651 Grade 2: 4% vs. 17% p=0.01	**T stage** In multivariate analysis T1 stage strongly affected OS (OR 5.13, 95% CI 1.06 to 24.83, p=0.042) **Stage IA pts:** **OS:** P=0.499 **CSS:** P=0.386 **DFI:** P=0.531 **OS rates:** At 1 yr: 95% vs. 100% At 2 yrs: 81% vs. 97% At 5 yrs: 52% vs. 62%	WR was better except than for Stage 1A pts for whom it was the same.
Safi, 2015 [19]	RFA vs. SLR vs. RT SLR vs. RFA:	**OS:** SLR vs. RFA: HR[a], 2.72, 95% CI, 0.77 to 9.59; p=0.121	**PFS**: SLR vs. RFA: HR[a], 1.79, 95% CI, 0.82 to 3.92; p=0.143	SLR vs. RFA: **PR*:** HR[a], 7.57, 95% CI, 1.94 to 29.47; p=0.004 **LR:** HR[a]:3.62, 95% CI, 1.29 to 10.2; p=0.015 **Regional recurrence:** HR[a]:1.73, 95% CI, 0.37 to 8.11; p=0.489 **DR:** HR[a]:1.11, 95% CI, 0.32 to 3.80; p=0.875	NR	Comparative data NR	NR	After adjustment for age and tumour size no difference in OS or PFS. There were differences in PR.
Ezer, 2014 [20] **ABS**	RFA vs. RT	**OS:** HR 0.93; 95% CI: 0.62 to 1.40, p=NS **CSS:** HR 0.72; 95% CI: 0.36 to1.46, p=NS	NR	NR	NR	NR	**Tumours ≤3 cm** **OS:** HR: 0.74; 95% CI: 0.44 to 1.24, p=NS **CSS:** HR: 0.743; 95% CI: 0.14 to 1.35, p=NS	RFA and RT are equivalent in older pts with early stage NSCLC

Author, year, (ref)	Intervention and comparison	OS, CSS, Mortality/morbidity	Disease control (e.g., PFS, DFI)	Recurrence	Risk factors, predictors of outcome	LOS and AE	Subgroups	Authors conclusions
Kwan, 2014 [21]	RFA vs. SLR	**OS*** (adjusted for pt, tumour and treatment): HR: 1.154 (95% CI:0.717 to 1.858), p=0.555 **CSS** (adjusted for pt, tumour and treatment, and time-dependent variables): HR: 1.815 (95% CI: 1.074 to 3.067), p=0.026	NR	NR	Comorbidity index: 1: HR 0.878 (0.554 to 1.392); >1: HR 0.881 (0.540 to 1.437), p=0.848[b]	NR	**Females** had lower risk of death (HR 0.667, P<0.0006). **Older** pts had worse survival: (HR range: 1.122 to 2.708, p<0.0001). **Stage 1B** pts had worse survival compared to pts with stage 1A (HR 1.277, p=0.037) **Histologic subtype:** Pts with squamous cell carcinomas (HR 1.385, p<0.0001) or not specified histologic type (HR 2.084, p<0.0001) had higher hazard of death.	After controlling for selection bias no difference was found in OS between sublobar resection and RFA.
Alexander, 2013b [22]	RFA vs. surgery	**OS** rates (RFA vs. Surgery): At 1 yr: 91% vs. 100% At 2 yrs: 73% vs. 95% At 3 yrs: 55% vs. 83% (Wilcoxon X^2=8.0225, p=0.0046) **CSS**: rates (RFA vs. Surgery): at 30 mos (estimated from figure): 68% vs. 90%	**Time to recurrence** was longer for pts in the surgical group (Wilcoxon X^2=5.3616, p=0.0206)	NR	NR	**LOS**: was significantly shorter for pts in the RFA group (Wilcoxon X^2 =77.0051, p<0.0001). **AE (Ig vs. Cg)** Gastrointestinal 12.5% vs. 10.71%; Respiratory 32.14% vs. 17.86%; Cardiac 16.07% vs. 14.29%; Secondary therapy 25% vs. 28.57%.	**Pts receiving adjuvant chemotherapy:** Pts who received surgery lived longer regardless treatment with adjuvant chemotherapy (Wilcoxon X^2=8.2736, p=0.0407). TTR was no different for this subgroup of pts (Wilcoxon X^2=5.9060, p=0.1163).	Pts in the surgical group showed a significant increase in survival, however the RFA pts were significantly older.

Author, year, (ref)	Intervention and comparison	OS, CSS, Mortality/morbidity	Disease control (e.g., PFS, DFI)	Recurrence	Risk factors, predictors of outcome	LOS and AE	Subgroups	Authors conclusions
Studies of Lung Metastases								
Tselikas, 2015 [23] **ABS**	surgery vs. RFA	**OS** rates: At 1 yr: 94.8% vs. 94% At 3 yrs: 67.2% vs. 72.1%, p=0.46	**PFS** rates: At 1 yr: 49.4% vs. 38.9% At 3 yrs: 26.2% vs. 14.8%, p=0.18	**Local recurrence** rates: At 1 yr: 5.4% vs. 14.8% At 3 yrs: 10.6% vs. 18.6%, p=0.07 **Pulmonary progression**: At 1 yr: 39.1% vs. 41.2% At 3 yrs: 56% vs. 65.3%, p=0.99	NR	**Hospital stay** Significantly shorter for RFA pts: P<0.0001 **AE** rate for surgery vs. RFA: 29% vs. 32%, p=0.8	NR	RFA is efficient and safe and can be considered as an alternative to surgery for pts with lung metastases
Studies of Primary Lung Cancer and Lung Metastases								
Matsui, 2012 [24][c]	Cases: phrenic nerve injury Controls: no injury	NR	NR	NR	**Risk factors:** Distance from phrenic nerve <10 mm: OR 66.8 (95% CI: 8.84 to 504.2), p<0.001 Size ≥20 mm : OR 3.01 (95% CI: 0.36 to 24.8), p=0.307	Phrenic nerve injury incidence: 1.3%	NR	Proximity of the tumour to phrenic nerve was an independent risk factor for nerve injury.

* Primary end point

[a] HR adjusted for age and tumour size.

[b]Results of an additional analysis on 69 pts using propensity score matching.

[c]This study is listed in the table of comparative studies, however it does not compare different interventions.

AE = adverse events; Cg = control group; CI = confidence interval; CSS = cancer-specific survival; DFI = disese-free interval; DR = distant recurrence; ds = days; FEV1 = predicted forced expiratory volume; FFR = freedom from recurrence; HR = hazard ratio; Ig = intervention group; LOS = length of hospital stay; LR = local recurrence; mos = months; NR = not reported; NS = not significant; NSCLC = nonsmall cell lung cancer; OR = odds ratio; OS = overall survival; PR = primary tumour recurrence; Pts = patients; RFA = radiofrequency ablation; RT = radiotherapy; SLR = sub-lobar resection; WR = wedge resection; yrs = years.

Table 4c. Summary of quality assessment of included comparative, fully published, trials of radiofrequency ablation, based on the Cochrane ROBINS tool [4]

Study	*Risk of bias judgement*			
	Low	Moderate	Serious	Critical
Studies of Primary Lung Cancer				
Ambrogi, 2015 [18]				✓
Safi, 2015 [19]				✓
Kwan, 2014 [21]		✓		
Alexander, 2013b [22]			✓	
Studies of Primary Lung Cancer and Lung Metastases				
Matsui, 2012 [24]				✓

Cryoablation

The systematic review by Lee et al. [16] included studies of endoscopic cryotherapy of endobronchial tumours performed with palliative intent; some of the studies included inoperable patients with early and others with advanced disease. The authors included 15 case studies and one comparative observational study published from 1981 to 2008. The studies included in this review were very heterogeneous not allowing any firm conclusions.

Our systematic review did not identify any comparative studies. Since no higher quality evidence was found, 11 noncomparative studies were included; two examined patients with primary lung cancer [56,57], three examined patients with lung metastases [58-60], and six patients with both primary and metastatic lung cancer [61-66]. Four of these studies were published as conference abstracts [60,61,64,65], and they will not be discussed any further. The methodologies of the included studies were varied and procedures were not standardized. Tables 2a and 2b in Appendix 6 present the general characteristics and the results of these studies.

Outcomes: Cryoablation

Question 1: "What is the effectiveness of CRYO for the treatment of patients with early-stage primary lung cancer or lung metastases?"

Patients with primary lung cancer

In patients with primary, early-stage lung cancer, CRYO was performed with curative intent; a retrospective case series [56] and a survey [57] reported data on survival, disease control, and recurrence.

Patients with metastatic disease

In patients with metastatic disease, CRYO was performed either with curative or palliative intent: a retrospective case series [58], and a prospective single arm study [59] reported on survival, disease control, response, and quality of life. As with for patients with primary disease, the results are heterogeneous and no conclusions can be drawn (see numerical results in Appendix 6, Table 2b

Patients with primary or metastatic disease

Three fully published case series [62,63,66] included patients with primary or metastatic disease and reported on disease control [62,63], progression [65], and technical success [62] (see numerical results in Appendix 6, Table 2b).

For all the patient populations, these studies were of poor quality and presented very heterogeneous results from which no conclusions can be drawn (see numerical results in Appendix 6, Table 2b).

Question 2: "What are the complications associated with CRYO for early-stage primary lung cancer or lung metastases?"

The most frequent complications identified in the systematic reviewy by Lee et al. [16] were hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea (reported in 10 of 16 studies).

Our systematic review of primary studies included three fully published noncomparative studies that reported on adverse events [56,59,66]. Adverse events that were reported were major events such as deaths, grade 3 events, pneumothorax, hemoptysis, and pleural effusion (see numerical results in Appendix 6, Table 2b).

Question 3: "What patient populations are most likely to benefit from CRYO for early-stage primary lung cancer or lung metastases?"

Patients with primary lung cancer

Gao et al. [57] reported no statistically significant difference in OS between patients with early versus later stage cancer, between patients with tumours of different histology (nonsmall cell lung cancer [NSCLC] versus small cell lung cancer [SCLC]), and between patients treated with cryotherapy and traditional Chinese medicine (TCM) and patients treated with TMC, or CRYO and a targeted drug. The same authors reported that patients who received CRYO in combination with TCM alone had a better OS than patients who received CRYO and TCM plus chemotherapy or radiotherapy. Detailed numerical results are reported in Table 2b in Appendix 6.

Patients with primary lung cancer and lung metastases

Tumour size. Littrup et al. [61] found that among patients treated with CRYO, those who had tumours ≤3 cm were experiencing statistically significantly less adverse events than those who had tumours >3 cm (Appendix 6, Table 2b).

Tumour position. Zhikai et al. [62] reported that patients with endothracheal tumours had a significantly shorter PFS than patients with extratracheal tumours or with tumours located on the tracheal wall. Numerical results are reported in Appendix 6, Table 2b.

Tumour histology. Zhikai et al. [62] reported that patients with NSCLC had a significantly longer PFS than patients with SCLC, and that patients with medium- or well-differentiated tumours had statistically significantly longer PFS than patients with poorly differentiated tumours.

Microwave ablation

For all questions, the Working Group used the 2013 NICE report [6], and supplemented this evidence with a search for primary studies from 2013 to December 2015.

The systematic review by NICE [6] included seven retrospective case series [15,67-72], published between 2006 and 2013 with 339 patients, and three case reports [73-75], published from 2008 to 2013; it is available at: https://www.nice.org.uk/guidance/ipg469.

NICE issued recommendations based on the results of their systematic review, that the procedure should be used with special arrangements for clinical governance, consent and audit, because of the uncertainty of the evidence base.

Our systematic review identified four fully published retrospective case series on MWA published from 2013 to 2015. Two examined patients with primary lung cancer [76], and three studied patients with primary or metastatic disease [77-79]. Tables 3a and 3b in Appendix 6 present the general characteristics and summary results of these studies.

Outcomes: Microwave ablation

Question 1: "What is the effectiveness of MWA for the treatment of patients with early stage primary lung cancer or lung metastases?"

Patients with primary lung cancer

Survival. Among the case series identified by the systematic review by NICE [6], 48 patients with NSCLC [68] reported OS rates of 75%, 54%, and 29%, respectively, at one, two, and three years.

In a recent case series of 47 patients identified by our systematic review, median OS was 33.8 months (95% CI, 31.9 to 35.7 months), and OS rates were 89%, 63%, 43%, and 16% at one, two, three, and five years, respectively [76]; median CSS was 47.4 months [76].

Disease control. In the case series of 47 patients identified by our systematic review, median TTR was 45.5 months [76].

Recurrence. In the case series of 47 patients identified by our systematic review, [76] local progression rate was 27.7%.

Patients with primary lung cancer and lung metastases

Survival. Among the case series identified by the systematic review by NICE [6], a study of 21 patients with pulmonary metastatic tumours [68] reported OS rates of and 48%, 24% and 14% at one, two and three years respectively; and a study of 50 patients [70] reported OS rates at one, two, and three years 65%, 55% and 45% respectively.

None of the studies in our systematic review reported results for this outcome.

Disease control. A case series of 69 patients [68], identified by the review by NICE [6], reported recurrence-free rates of 73%, 50%, and 27% at one, two, and three years, respectively, for patients with NSCLC (n=48) and 48%, 19%, and 14% for patients with pulmonary metastatic tumour (n=21), respectively. Another case series of 80 patients by Vogl et al. [80], identified by the NICE guideline [6], reported a mean time to tumour progression after ablation of six months; a more recent study by the same author, identified by our review, reported a mean time to tumour progression of 8.3±5.5 months [79].

Recurrence. Among the case series identified by the review by NICE [6], Wolf et al. reported that 26% (13 of 50) of patients had recurrent disease at the ablation site at six months' post-ablation, and 22% (11 of 50) had distant recurrent disease at 10 months' follow-up [70].

Among the case series identified by our systematic review, Vogl et al. reported a median local progression of 22.6±12.4 months, and a local progression rate of 33% of the tumours [79].

Other outcomes

Re-treatment. In a case series of 80 patients identified by the systematic review by NICE [6], re-ablation of residual or recurrent lesions was reported in 49% (17 of 35) of lesions. Secondary tumour control after re-ablation was reported successful in 53% (9 of 17) of these lesions, with no residual or recurrent tumour (within 6- to 9-month follow-up) [80].

Technical success: Vogl et al. [79] reported a technical success rate of 92.3%.

Question 2: "What are the complications associated with MWA for early-stage primary lung cancer or lung metastases?"

Patients with primary lung cancer

The case series by Yang et al. [76] reported at least one adverse event in over one-half of the patients treated, with pneumothorax being the most frequent complication experienced by patients. Similar results were reported by March et al. [81] in an abstract publication. See numerical results in Appendix 6, Table 3b.

Patients with primary lung cancer and lung metastases

Among the case series included in the NICE report [6], the study by Lu et al. [68] and Vogl et al. [67] reported no deaths during or within 30 days of the procedure. On the other hand, the study by Splatt et al. [77], identified by our review, reported 1.4% mortality within 30 days of the intervention.

In the case series identified by the NICE report [6], pneumothorax was reported in 9% of the procedures in patients with pulmonary metastases [67], hemothorax was reported in 3% of patients treated [68], and hemoptysis was reported in 7% of patients [68].

Adverse events related to technical issues were reported in two studies included in the NICE report [6]. One case of needle tip fracture over 23 patients was reported in a case series [72], and a microwave antenna breakage was reported in a case report [75]; in both instances the breakage happened when the applicator was withdrawn.

Among the studies included in our review, the rates of adverse events varied, and were reported in approximately 20% of ablations [77,78]. Among the most common adverse events reported were pneumothorax, pleural effusion, and pain (see numerical results in Appendix 6, Table 3b).

Question 3: "What patient populations are most likely to benefit from MWA for early-stage primary lung cancer or lung metastases?"

The study by Lu et al. [68] included in the NICE report [6] compared OS and recurrence-free survival at one, two, and three years between patients with NSCLC and metastatic disease and found a statistically significant difference in favour of NSCLC patients (p=0.02) for both outcomes. The same authors found a statistically significant difference in local tumour progression in tumours >4 cm in diameter compared with <3 cm (p=0.04) and 3–4 cm (p=0.03).

Among the studies included in our systematic review, March et al. [81], in an abstract publication, compared patients with primary lung tumours <3 cm with patients with tumours >3 cm, and found that technical success, adverse events, and recurrence rate were statistically significantly better for smaller lesions (Appendix 6, Table 3b). Yang et al. [76] also reported a significantly better survival for patients with tumours ≤3.5 cm as compared with tumours >3.5 cm (Appendix 6, Table 3b).

Ongoing, Unpublished, or Incomplete Studies

Four abstracts of interim results were identified for radiofrequency ablation [82-85] and one for cryotherapy [86], and were excluded. More details are reported in Appendix 6, Table 4).

The search of the clinicaltrials.gov registry identified 13 trials that are still ongoing. Two among those are randomized controlled trials of RFA and CRYO (Table 5).

Table 5. Ongoing trials as of March 24, 2016

#	Interventions Design	Official title	Status	Protocol ID	Completion Date	Last updated
1	RFA and External Beam radiation Single group assignment	A Phase II Study of Radiofrequency Ablation Combined With External Beam Radiation Therapy for Patients With Medically Inoperable Non-Small Cell Lung Cancer (Stage Ia and Select Ib) and the Predictive Value of Positron Emission Tomography	Ongoing, but not recruiting participants	NCT00499447	March 2010	September 2015
2	RFA Single group assignment	A Pilot Study of Radiofrequency Ablation in High-Risk Patients With Stage IA Non-Small Cell Lung Cancer	Ongoing, but not recruiting participants	NCT00109876	July 2010	July 2015
3	RFA Observational	A Prospective Study of Outcomes of Radiofrequency Ablation of Lung Tumors	Has suspended recruitment	NCT00280189	December 2020	April 3, 2015
4	Ablation and surgery Single arm	The EMPrint™ Ablate and RESect Study in Patients With Metastatic Lung Tumors (EMPRESS)	Recruiting participants	NCT02323854	December 2017	December 2015
5	MWA Single group assignment	MARK 1A Series: Percutaneous Microwave Ablation for Patients With Lung Tumor(s)	Not yet recruiting	NCT02673021	February 2018	January 2016
6	RFA Single Group Assignment	Phase II Study Evaluating Safety and Efficacy of Stereotactic Body Radiotherapy and Radiofrequency Ablation for Medically Inoperable and Recurrent Lung Tumors Near Central Airways	Recruiting participants	NCT01051037	August 2017	March 2016
7	RFA Randomized, double blind	Application of CPAP to Reduce Complications and Improve Treatment of Radiofrequency Ablation of Lung Cancer Under Conscious Sedation. A Randomized Study	Recruiting participants	NCT02117908	December 2017	August 2015
8	RFA Observational	A Prospective Study of Radiofrequency Ablation Combined With Chemotherapy for Pulmonary Tumors	Unknown	NCT01105182	June 2011	December 2009
9	RFA Single Group Assignment	Radiofrequency Ablation in Resectable Colorectal Lung Metastasis: A Phase-II Clinical Trial	Ongoing, but not recruiting participants	NCT00776399	August 2017	July 2015
10	Cryotherapy or RFA Randomized, single blind	A Prospective Study of Ablation of Pulmonary Focal Pure Ground Glass Opacity (Randomized controlled trial)	Unknown	NCT01429649	December 2014	September 2011
11	RFA Single Group Assignment	Efficacy and Safety of Radiofrequency Ablation of Malignant Pulmonary Nodules	Ongoing, but not recruiting participants	NCT02629978	October 2020	October 2015
12	Erlotinib and Local Therapies including surgical resection, stereotactic radiosurgery, ablation and conventional radiation therapy	Pilot Study of Local Therapies for Oligometastatic Non-Small Cell Lung Cancer Harboring Sensitizing EGFR Mutations	Recruiting participants	NCT02450591	May 2017	March 2016

	Single Group Assignment					
13	Hepatic and/or pulmonary resection, radiofrequency ablation (RFA), transcatheter arterial chemoembolization, CyberKnife stereotactic radiosurgery Prospective cohort	Intervention to Hepatic and Pulmonary Metastasis in Breast Cancer Patients: Prospective, Observational, Multi-institutional Registration Study - IMET	Recruiting participants	NCT02251353	June 2022	September 2014

DISCUSSION

Radiofrequency ablation

A previous systematic review of noncomparative studies [17] noted an evolution of RFA techniques over time. However, previous guidelines [5,7,8,10] and systematic reviews [17] did not identify any comparative studies, therefore no conclusions could be drawn about the efficacy and the safety of RFA.

Ulike previous systematic reviews, we were able to identify five published comparative studies [18-22], and two ongoing randomized trials of RFA (NCT02117908 and NCT01429649). However, the included comparative studies were mostly retrospective, clinically heterogeneous, and their quality was variable, thus preventing definite conclusions about the efficacy and safety of this procedure.

Two comparative studies on RFA used the SEER registry linked to MEDICARE data [19,20], while the others used institutional data collected ad hoc. These two types of evidence provide data with different granularity: the SEER studies including a very large number of patients, but lacking information specific to the individual settings (e.g., why patients were chosen for a specific treatment, what the experience of the operators was etc.), while the institutional studies had relatively small sample sizes but more information on settings and individual patients and interventions.

In patients with primary lung cancer, studies that controlled for selection bias [19-21] showed no statistically significant difference in survival and disease control for patients treated with surgery and RFA, while studies that did not control for confounders [18,22] showed more favourable outcomes for surgical patients. Local recurrence was significantly higher in patients treated with RFA in all studies [18,19,23], while distant recurrence was similar between groups [18,19]. Patients treated with RFA may need more than one RFA procedure to completely ablate the tumour and, thus, secondary technique effectiveness may be greater than primary technique effectiveness, but no data on this were available from our systematic review or from previous ones.

Patients with primary lung tumours in stage IA, and patients with tumours <3 cm, although based on evidence of lower strength, showed similar survival and disease control in both comparative and noncomparative studies [18,20,21,25,29,31,36,40,41,44,51]. Older patients were shown to have worse survival and females had lower risk of death [21]. Length of hospital stay was shorter for RFA compared with surgery in the studies that reported this outcome.

Less data were available for patients with lung metastases. In an abstract publication, OS was not different between surgery and RFA in these patients [23].

Procedural mortality of RFA has been reported to be very low. The most common among adverse effects of RFA was pneumothorax [17,27,29,30,33,34,39-42,46,53,55]. Among the risk factors for pneumothorax were old age, male gender, and a larger number of ablated tumours [12]. However, the nature of the adverse events may likely to be different with surgery and RFA.

Cryoablation

The only identified sytematic review on CRYO [16] included studies of endoscopic cryotherapy for endobronchial tumours that were treated with palliative intent.

Our search identified 11 noncomparative trials, of intra-parenchymal CRYO, often used with curative intent [56,57,59,62,63,66], and an ongoing randomized trial comparing cryotherapy with RFA (NCT01429649). Reported major adverse events were death, grade 3 events, pneumothorax, hemoptysis, and pleural effusion. At this time it is impossible to draw conclusions from this body of evidence.

Microwave ablation

The systematic review by NICE [6] included seven retrospective case series [15,67-72] and three case reports [73-75]. Our systematic review identified five more recent retrospective case series [76-79,81], one of which was an abstract publication. No comparative studies were identified even among the ongoing trials. At this time it is impossible to draw conclusions from this body of evidence.

Limitations

The included studies were not randomized, and their sample sizes were relatively small; interventions and populations were heterogeneous, thus rendering it impossible to draw conclusions from this body of evidence.

We measured the quality of the few studies that were comparative, and risk of bias was judged to be serious in one study, moderate in one study, and critical in two studies. The studies that were not comparative yielded low-quality evidence because of their design.

CONCLUSIONS

Percutaneous ablative therapies are relatively new technologies; RFA is somewhat established, with a firmer evidence base than CRYO and MWA. However, the evidence base for these ablative modalities is expected to become stronger in the near future.

INTERNAL REVIEW

The evidence summary was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made.

Approval by the Interventional Oncology Steering Committee

After internal review, the report was presented to the Interventional Oncology Steering Committee. The Interventional Oncology Steering Committee reviewed the document at a meeting held in Toronto, Ontario, on August 5, 2016, and formally approved the document.

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Appendix 1: Members of the Working Group and their Conflict of Interest declaration

Members	Role	Conflict of Interest
John Kachura	Co-Chair	Past President of CIRA (Canadian Interventional Radiology Association). The Following parties contribute financially to CIRA: Abbott Vascular, Angiodynamics, Bard, Boston Scientific, Cook Medical, Cardis Endovascular, Covidier, GE Healthcare, Gore, InterV Medical, Medtronic and Philips
		Co-applicant for patent regarding an invention for thermal therapy
		Investigator in a sponsored research agreement between University Health Network and Bard regarding thermal therapy invention.
Sriharsha Athreya	Member	(Temporary Consultant to Boston Scientific on Angiojet for fistula and DVT thrombectomy)
Mehran Midia	Member	None declared
Richard Malthaner	Member	None declared
Fulvia Baldassarre	Member	None declared

Appendix 2: A) Literature Search Strategy: Systematic reviews

Radiofrequency ablation

Database: Ovid MEDLINE(R) without Revisions <1996 to September Week 4 2015>, Ovid MEDLINE(R) Daily Update <October 05, 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 05, 2015>
Search Strategy:
---
1 ((radiofrequenc* or radio-fre- quenc* or radio frequenc*) adj4 (ablation* or therap* or treat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2 (RFTA or RFA or RFT or RFCA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3 ((focal adj2 ablat*) or (thermal adj2 ablat*)).tw.
4 ((microwave adj2 ablat*) or MWA).tw.
5 Cryosurgery/
6 cryoablation:.mp.
7 (thermotherapy or cryoablation or cryosurgery).mp. or cryosurgery/ or exp Hyperthermia, Induced/
8 exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
9 or/1-8
10 (systematic adj (review: or overview:)).mp.
11 (meta-analy: or metaanaly:).mp.
12 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
13 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
14 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
15 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
16 or/10-15
17 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
18 (stud: adj1 select:).ab.
19 (17 or 18) and review.pt.
20 16 or 19
21 (guideline or practice guideline).pt.
22 exp consensus development conference/
23 consensus/
24 (guideline: or recommend: or consensus or standards).ti.
25 21 or 22 or 23 or 24
26 20 or 25
27 (comment or letter or editorial or note or short survey or news or newspaper article or case report or historical article).pt.
28 animal/ not human/

29 (lung adj2 (cancer$ or Neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp. or SCLC.tw. or NSCLC.tw.
30 exp lung neoplasms/
31 29 or 30
32 27 or 28
33 9 and 26 and 31
34 33 not 32

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Database: Embase <1996 to 2015 Week 40>
Search Strategy:
---
1 (systematic adj (review: or overview:)).mp.
2 (meta-analy: or metaanaly:).mp.
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
7 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
8 (stud: adj1 select:).ab.
9 (7 or 8) and review.pt.
10 or/1-6
11 9 or 10
12 consensus development conference/
13 practice guideline/
14 *consensus development/ or *consensus/
15 *standard/
16 (guideline: or recommend: or consensus or standards).kw.
17 (guideline: or recommend: or consensus or standards).ti.
18 or/12-17
19 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
20 (11 or 18) not 19
21 ((radiofrequenc* or radio-frequenc* or radio frequenc*) adj4 (ablation* or therap* or treat*)).mp.
22 (RFTA or RFA or RFT of RFCA).mp.
23 ((focal adj2 ablat:) or (thermal adj2 ablat:)).tw.
24 ((microwave: adj2 ablat:) or MWA).tw.
25 Cryosurgery/
26 cryoablat:.mp.
27 (thermotherapy or cryoablation or cryosurgery).mp. or exp Hyperthermia, Induced/
28 exp microwave radiation/
29 coagulation therapy.mp.
30 electrocoagulation/

31 animal/ not human/
32 (lung adj2 (cancer$ or Neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp. or SCLC.tw. or NSCLC.tw.
33 exp lung cancer/th [Therapy]
34 or/21-30
35 32 or 33
36 20 and 34 and 35

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>
Search Strategy:
---
1 ((radiofrequenc* or radio-fre- quenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]
2 (RFTA or RFA or RFT or RFCA).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]
3 ((focal adj2 ablat:) or (thermal adj2 ablat:)).tw.
4 (microwave adj2 ablat:).tw.
5 (cryoablation: or cryosurgery).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]
6 (thermotherapy or cryoablat: or cryosurgery).mp.
7 coagulation therapy.mp.
8 (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp. or SCLC.tw. or NSCLC.tw.
9 or/1-7
10 8 and 9

****

Appendix 2: B) Literature Search Strategy: Primary studies

Radiofrequency ablation
Database: Ovid MEDLINE(R) Daily Update <January 6, 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1. ((radiofrequenc* or radio-frequenc* or radio frequenc*) adj4 (ablation* or therap* or treat*)).mp.
2. (RFTA or RFA or RFT or RFCA).mp.
3. ((focal adj2 ablat*) or (thermal adj2 ablat*)).tw.
4. thermotherapy.mp. or exp Hyperthermia, Induced/
5. (lung adj2 (cancer$ or Neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
6. exp lung neoplasms/
7. 5 or 6
8. 1 or 2 or 3 or 4
9. 7 and 8
10. limit 9 to (english language and yr="2009 -Current")
****

Database: Embase <1996 to 2016 Week 1>
Search Strategy:

1. ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
2. (RFTA or RFA or RFT of RFCA).mp.
3. ((focal adj2 ablat:) or (thermal adj2 ablat:)).tw.
4. 1 or 2 or 3
5. (lung adj2 (cancer$ or Neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp. or SCLC.tw. or NSCLC.tw.
6. exp lung cancer/th [Therapy]
7. 5 or 6
8. 4 and 7
9. limit 8 to (english language and yr="2009 -Current")
****

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2016>
Search Strategy:
---
1. ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
2. (RFTA or RFA or RFT or RFCA).mp.
3. ((focal adj2 ablat:) or (thermal adj2 ablat:)).tw.
4. 1 or 2 or 3
5. (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp. or SCLC.tw. or NSCLC.tw.
6. 4 and 5
7. limit 6 to (yr="2009 -Current" and english language)

Cryotherapy:
Database: Ovid MEDLINE(R) Daily Update <November 18, 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp Cryotherapy/
2 exp Cryosurgery/
3 (thermotherapy or cryoablat: or cryotherapy or cryosurgery).mp.
4 1 or 2 or 3
5 exp Lung Neoplasms/
6 (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
7 (SCLC or NSCLC).tw.
8 5 or 6 or 7
9 4 and 8

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2015>
Search Strategy:
---
1 exp Cryotherapy/
2 exp Cryosurgery/
3 (thermotherapy or cryoablat: or cryotherapy or cryosurgery).mp.
4 1 or 2 or 3
5 exp Lung Neoplasms/
6 (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
7 (SCLC or NSCLC).tw.
8 5 or 6 or 7
9 4 and 8
10 limit 9 to (yr="2008 -Current" and english language)

Database: Embase <1996 to 2016 Week 1>
Search Strategy:
---
1 exp cryotherapy/
2 exp cryosurgery/
3 (thermotherapy or cryoablat: or cryotherapy or cryosurgery).mp.
4 1 or 2 or 3
5 exp lung cancer/
6 exp lung tumor/
7 (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
8 (SCLC or NSCLC).tw.
9 5 or 6 or 7 or 8
10 4 and 9
11 limit 10 to (english language and yr="2008 -Current")

Microwave ablation

Database: Ovid MEDLINE(R) Daily Update <January 6, 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

1. (lung adj2 (cancer$ or Neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
2. exp lung neoplasms/
3. 1 or 2
4. ((microwave adj2 ablat*) or MWA).tw.
5. thermotherapy.mp. or exp Hyperthermia, Induced/
6. exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
7. 4 or 5 or 6
8. 3 and 7
9. limit 8 to (english language and yr="2013 -Current")

****
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2016>
Search Strategy:

1. (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp. or SCLC.tw. or NSCLC.tw.
2. ((focal adj2 ablat:) or (thermal adj2 ablat:)).tw.
3. (microwave adj2 ablat:).tw.
4. coagulation therapy.mp.
5. 2 or 3 or 4
6. 1 and 5
7. limit 6 to (yr="2013 -Current" and english language)

****

Database: Embase <1996 to 2016 Week 1>
Search Strategy:

1. (lung adj2 (cancer$ or Neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
2. exp lung cancer/
3. exp lung tumor/
4. (lung adj2 (cancer$ or neoplas$ or adenocarcin$ or carcin$ or malig$ or tumo$)).mp.
5. (SCLC or NSCLC).tw.
6. 1 or 2 or 3 or 4 or 5
7. ((microwave adj2 ablat*) or MWA).tw.
8. hyperthermic therapy/
9. microwave radiation/ or electrocoagulation/
10. 7 or 8 or 9
11. 6 and 10
12. limit 11 to (english language and yr="2008 -Current")

Appendix 3: Study selection criteria

Study Selection Criteria

A) Systematic reviews, or guidelines that included a systematic review, were eligible for inclusion if they met all the following criteria:

Included:

- Systematic reviews that included studies of adult patients with early-stage primary lung cancer or lung metastases.
- Systematic reviews with a research question looking at focal tumour ablation.
- Systematic reviews that examine the effectiveness of thermal ablation including, radiofrequency ablation (RFA), cryoablation (CA), and microwave ablation (MWA).
- Systematic reviews with a search strategy dated 2008 or later.
- Systematic reviews that include RCTs, or RCTs and non-randomized comparative studies for efficacy questions

Excluded:

- If focal tumour ablation is only used as a comparison, but the review focus is on another strategy, and the discussion of these treatment modalities is tangential.
- Studies that are not systematic reviews (i.e., reviews that do not have a specific question and did not state inclusion/exclusion criteria)
- Systematic reviews in language other than English.
- Systematic reviews with a search cut-off prior to 2008.
- Systematic reviews that do not report enough data (i.e., protocols, abstracts of systematic reviews).
- Systematic reviews that compare different modalities of the same focal tumour ablation technique.
- Systematic reviews of high intensity focused ultrasound (HIFU).
- Systematic reviews of laser interstitial thermal therapy (LITT).

B) Primary studies (only for gap areas from systematic reviews)

Included:

- Studies of patients with early-stage primary lung cancer or lung metastases.
- Thermal ablation including, RFA, CA, and MWA.
- Comparative and non-comparative studies, prospective and retrospective, with sample size ≥30.
- Studies that compared: Alternative treatments (e.g., surgery, radiation versus focal ablation), focal tumour ablation treatments versus other focal tumour ablation treatments (e.g., microwave ablation versus cryotherapy), and no therapy or supportive care (e.g., focal ablation versus watchful waiting).
- Studies published: in 2009 or afterward for RFA; in 2008 or afterward for Cryotherapy; and on 2013 or afterward for microwave ablation*.
- Studies that reported outcomes of survival, disease control, response, quality of life, and adverse events.

Excluded:

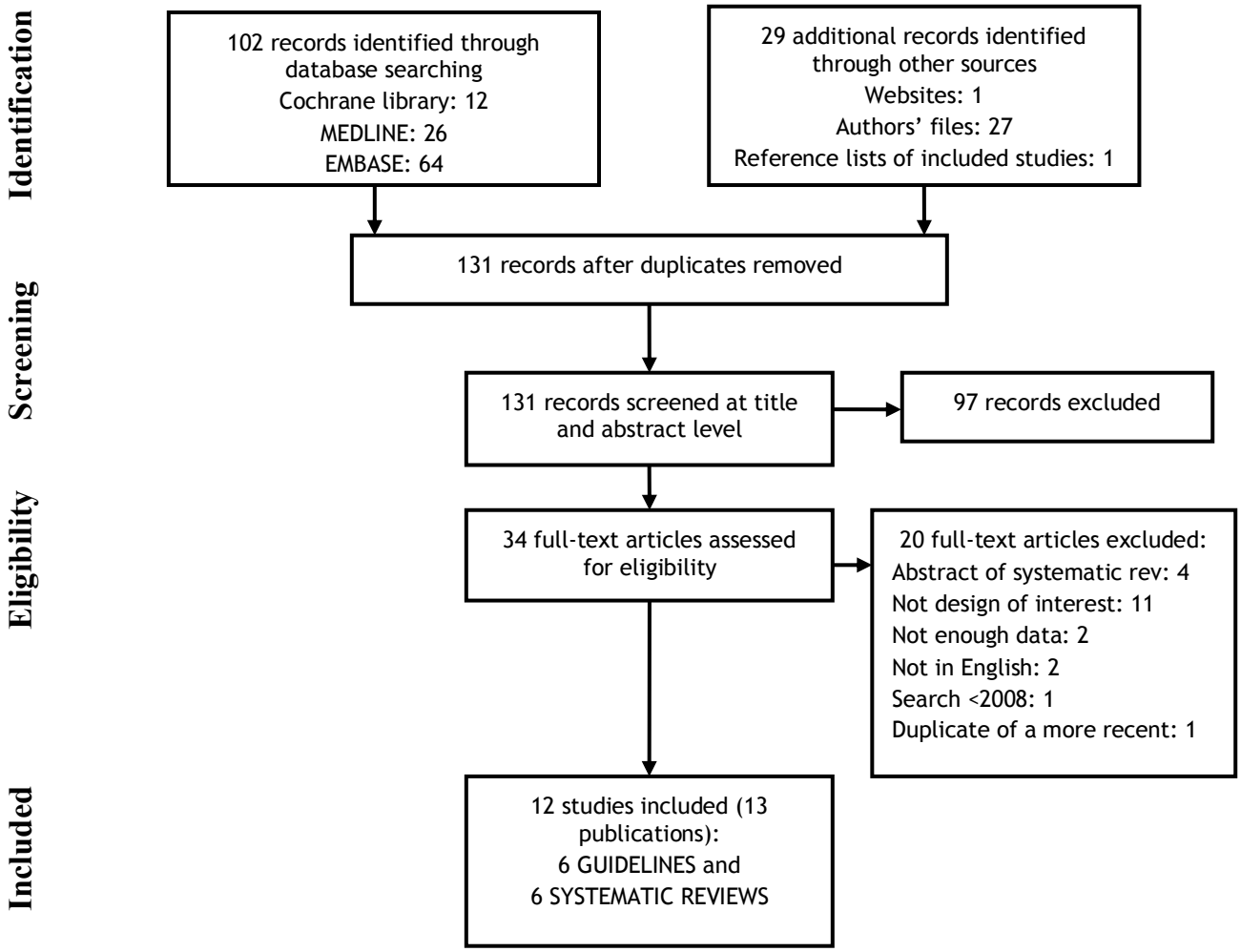
- Articles not in English.

- Articles that do not have a non-focal ablation comparison.
- Publications that do not provide enough data or not outcomes of interest (e.g., cost).
- Abstracts of interim analysis.
- Studies with a sample size <30 for efficacy questions.
- Editorials, news, commentaries, comments, and letters.

*Note: the search for primary studies will cover areas that were not discussed by systematic reviews (e.g., time periods, adverse events, or topics that the existing systematic reviews did not discuss). For this reason the cut off date is different for different interventions.

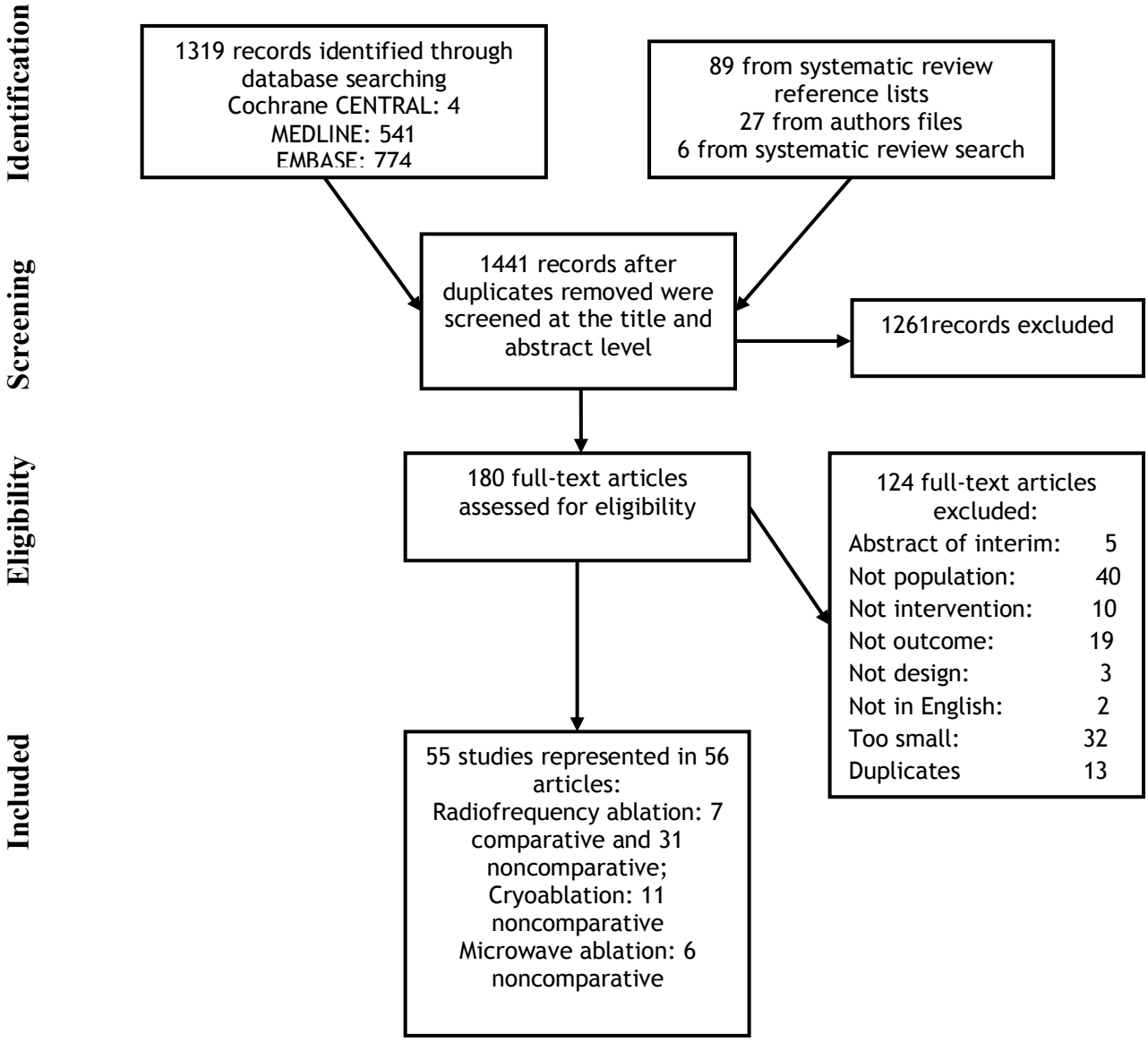
Appendix 4: PRISMA Flow Diagram

A) Focal Tumour Ablation of Lung Cancer: Study Flow Chart: Systematic reviews



aa

B) Focal Tumour Ablation of Lung Cancer: Study Flow Chart: Primary Studies



Appendix 5: Quality assessment of comparative studies on radiofrequency ablation with the Cochrane ACROBAT-NRSI tool

The ACROBAT-NRSI tool (1): At protocol stage

Specify the research question by defining a generic target randomized trial

Participants	Patients with early-stage lung cancer or lung metastases from other primary
Experimental intervention	Radiofrequency ablation
Control intervention	• Alternative treatments (e.g., surgery, radiation versus focal ablation) • Focal ablation treatments versus other focal ablation treatments (e.g., microwave ablation versus cryotherapy) • No therapy or supportive care (e.g., focal ablation versus watchful waiting).

Specify the nature of the target comparison (effect of interest)

e.g. effect of *initiating* intervention (as in an intention-to-treat analysis), or effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Effect of initiating intervention

List the confounding domains relevant to all or most studies

Bias due to confounding: e.g., performance status, tumour size, clinical stage. Follow-up times of different length. **Bias due to patients selection:** The radiofrequency ablation patients cannot be operated because they have contraindications, they were more frail.

List the possible co-interventions that could differ between intervention groups and could have an impact on study outcomes

Patients in one group may have received chemotherapy or radiation therapy, while patients in the other group did not. Patients may have received conscious sedation and local analgesia or general anesthesia.

The ACROBAT-NRSI tool (2): For each study:

Ambrogi et al. 2015 [18]

Specify a target trial specific to the study.

The protocol-specified target randomized trial fully applies	☐	*OR*	Participants	Patients with stage I lung cancer
			Experimental intervention	Radiofrequency ablation
			Control intervention	Wedge resection

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Rates of overall survival, cancer-specific survival (at 1, 2, and 5 years), and disease-free interval, recurrence rates: All were worse for the focal ablation group.

Specify the effect of interest

e.g. effect of *initiating* intervention (as in an intention-to-treat analysis), or effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Effect of initiating intervention

Specify the specific result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 [95% CI 0.83 to 2.77]) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Table 3b. Results of comparative studies of radiofrequency analysis

Preliminary consideration of confounders

a. Within each confounding domain listed in the review protocol, list the relevant variables, if any, measured in this study.

Bias due to confounding: Age (median [range]) was significantly older for radiofrequency ablation vs. wedge resection pts: 76 years (60-88) vs. 70 years (56-83), p=0.041; co-morbidities were higher in the radiofrequency ablation group , p<0.001; Performance status was worse in the radiofrequency ablation group.

Bias due to selection of patients: Patients had different prognosis in intervention and control groups.

b List additional confounding domains, if any, specific to the setting of this particular study. Within each domain, list the relevant variables, if any, measured in this study.

Time-varying confounding: Follow-up was split according to intervention received: Median 36 months for wedge resection and 42 months for radiofrequency ablation because patients in the radiofrequency ablation group came from a previous prospective institutional study while pts in the wedge resection group were retrospectively selected from the institution surgical database.

Bias in measurement of interventions. All authors were surgeons and outcome assessors were not blinded.

c List additional domains and corresponding measured variables, if any, that the study authors identified as potential confounders that are not included in the above domains.

Retrospective nature of the study. Lung function was better in the radiofrequency ablation group than in the wedge resection group.

Relationship between confounding domains and potential confounders.

In the table below, "critically important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Confounding domain	Is the domain critically important?*	Measured Variable	Did the authors demonstrate that controlling for this variable was unnecessary?*	Is the domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to move the effect estimate up or down? **
Bias due to counfounding: different age, performance status etc. Pts who undergo RFA are not fit for surgery	Yes	Age, sex, performance status, FEV_1% and FVC %, BMI and ACE-27 score	Yes – multivariate analysis showed no correlation with survival	Yes	Up
		T-stage	yes – T stage significantly affected survival P=0.042; OR 5.13; 95%CI 1.06-24.83		
		Patients in the intervention and control group had a different follow-up	Yes. Authors adjusted for baseline confounding. No factors predictors of outcome or predict a switch of interventions should have changed because patients were in two separate cohorts.		
Bias in measurement of interventions: Multiple studies (by same authors) include the same patients.	Yes	Authors do not report	No. Study by Ambrogi, 2011 included part of the patients (those treated with RFA)	No Information	No Information
Bias in measurement of interventions: Lack of implementation	Yes	Not measured	No	No Information	No information

fidelity (authors are thoracic surgeons)					

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

** For example, if the crude effect estimate is 1.3, adjustment to 1.6 is up, while adjustment to 0.7 is down. If the effect estimate is 0.7, adjustment to 1.1 is up while adjustment to 0.4 is down.

Abbreviations: FEV_1 - forced expiratory volume in 1 s; FVC = forced vital capacity; Pts = patients; RFA = radiofrequency ablation

Preliminary consideration of co-interventions

a. Are the (pre-specified) co-interventions likely to be administered in the context of this study?

Yes

b List additional co-interventions, if any, specific to the setting of this particular study.

None

Co-interventions

In the table below, "critically important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the variables fully measure the co-intervention, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Co-intervention	Is the co-intervention critically important?*	Did the authors demonstrate that controlling for this co-intervention was unnecessary?	Is the co-intervention measured validly and reliably?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
Radiotherapy	Yes	No information	No information	No information
Chemotherapy	Yes		No information	No information

Risk of bias assessment (cohort-type studies)

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	PN	T stage affected survival, and there are many confounding factors that have not been measured or taken into account.
	If N or PN to 1.1:		
	1.2. Were participants analyzed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding	Y	
	1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer questions 1.7 and 1.8, which relate to time-varying confounding	NA	
	If Y or PY to 1.2, or Y or PY to 1.3		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Y	Table 1

	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Y	
	1.6. Did the authors avoid adjusting for post-intervention variables?	Y	
	If N or PN to 1.2 and 1.3		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding?	NA	
	1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA	
	Risk of bias judgement	Critical	No information is provided on many potential confounders. Patients in the RFA group had co-morbidities that would impact on survival. The analysis showed that patients with stage T1a had the same outcomes as surgical ones.
	Optional: What is the predicted direction of bias due to confounding?	Favours comparator	T stage analysis showed that limiting to T1A no difference in survival was found.
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	N	Participants were from a previous study on RFA and from an institutional surgical database
	2.2. Do start of follow-up and start of intervention coincide for most subjects?	N	WR pts had a chest x-ray 3 months after, while RFA pts had CT scan at 1 months after
	2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y	They did a multivariate analysis.
	Risk of bias judgement	Critical	Pts in the RFA cohort had comorbidities that impacted on outcomes more than WR patients.
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours comparator	Patients in the focal ablation group were older and so much worse off that no matter what intervention, would die earlier anyways.
Bias in measure-ment of interventions	3.1 Is intervention status well defined?	PY	People in the RFA group had more than one intervention (up to 4 times)
	3.2 Was information on intervention status recorded at the time of intervention?	PY	Information came from already existing records.
	3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	PN	As above.
	Risk of bias judgement	Serious	Interventions were not matched in number for each lesion. A patient in the RFA group could get one or more applications
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours comparator	There is a need for multiple interventions for RFA to ablate the tumour as surgery does
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups?	NI	No information is provided on what the patients received
	4.2. Were numbers of switches to other interventions low?	Y	Switches impossible because RFA pts could not receive surgery
	4.3. Was implementation failure minor?	PY	Not reported

	4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these issues?	NA	
	Risk of bias judgement	Serious	The authors were all surgeons. Nothing is reported about operator expertise.
	Optional: What is the predicted direction of bias due to departures from the intended interventions?	Favours comparator	One can assume the operators had more experience with the surgery than with RFA.
Bias due to missing data	5.1 Are outcome data reasonably complete?	Y	
	5.2 Was intervention status reasonably complete for those in whom it was sought?	Y	
	5.3 Are data reasonably complete for other variables in the analysis?	Y	
	5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA	
	5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	NA	
	Risk of bias judgement	Low	No missing data
Bias in measurement of outcomes	6.1 Was the outcome measure objective?	PY	The authors were all surgeons, they may favour surgery, however the outcomes were OS and CSS.
	6.2 Were outcome assessors unaware of the intervention received by study participants?	PN	
	6.3 Were the methods of outcome assessment comparable across intervention groups?	PY	From retrospective chart review.
	6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	PY	Authors did not record how they did it.
	Risk of bias judgement	Critical	Many nonreported data.
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Favours comparator	Surgeons collecting data may well prefer the surgical option even unconsciously.
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain?	PN	
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	PY	
	7.3 ... different *subgroups*?	PN	
	Risk of bias judgement	Moderate	There is no protocol on which we can verify
	Optional: What is the predicted direction of bias due to selection of the reported result?	Favours comparator	They only report results that favour the surgery
Overall bias	**Risk of bias judgement**	Critical	
	Optional: What is the overall predicted direction of bias for this outcome?	Favours comparator	

CSS = cancer-specific survival; CT = computed tomography; N = no; NA = not applicable; NI = no information; OS = overall survival; PN = probably not; PY = probably yes; RFA = radiofrequency ablation; WR = wedge resection; Y = yes

The ACROBAT-NRSI tool (2): For each study:

Safi et al. 2015 [19]

Specify a target trial specific to the study.

The protocol-specified target randomized trial fully applies ☐ *OR*

Participants	Patients with stage I nonsmall cell lung cancer
Experimental intervention	Radiofrequency ablation
Control intervention	Sublobar resection or radiotherapy

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Time to primary tumour recurrence. Overall survival, progression-free survival

Specify the effect of interest

e.g., effect of *initiating* intervention (as in an intention-to-treat analysis), or effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Initiating the intervention and adhering to the intervention (they excluded from analysis cases without a definitive diagnosis.

Specify the specific result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g., RR = 1.52 (95% CI, 0.83 to 2.77) and/or a reference (e.g., to a table, figure or paragraph) that uniquely defines the result being assessed.

Table 3b

Preliminary consideration of confounders

a. Within each confounding domain listed in the review protocol, list the relevant variables, if any, measured in this study.

Bias due to confounding: E.g., performance status, tumour size, clinical stage. Follow-up times of different length.

Bias due to patients selection: The radiofrequency ablation patients cannot be operated because they have contraindications, are more frail.

b. List additional confounding domains, if any, specific to the setting of this particular study. Within each domain, list the relevant variables, if any, measured in this study.

Bias in measurement of outcomes: E.g., due to the high number of comparisons the p values were not adjusted are considered only descriptive.

c. List additional domains and corresponding measured variables, if any, that the study authors identified as potential confounders that are not included in the above domains.

None identified

Relationship between confounding domains and potential confounders.

In the table below, "critically important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Confounding domain	Is the domain critically important?*	Measured Variable	Did the authors demonstrate that controlling for this variable was unnecessary?*	Is the domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to move the effect estimate up or down? **
Bias due to confounding:	Yes	Age	No	Yes	Up
		Performance status	No		Up

		Tumour size	No		Up
		Clinical stage	No		Up
		Different length of follow-up	No Information	No information	No information
Bias due to pts selection	Yes	Not measured	No information	No information	No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

** For example, if the crude effect estimate is 1.3, adjustment to 1.6 is up, while adjustment to 0.7 is down. If the effect estimate is 0.7, adjustment to 1.1 is up while adjustment to 0.4 is down.

Preliminary consideration of co-interventions

a. Are the (pre-specified) co-interventions likely to be administered in the context of this study?

No information

b List additional co-interventions, if any, specific to the setting of this particular study.

General anesthesia

Co-interventions

In the table below, "critically important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the variables fully measure the co-intervention, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Co-intervention	Is the co-intervention critically important?*	Did the authors demonstrate that controlling for this co-intervention was unnecessary?	Is the co-intervention measured validly and reliably?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
Received chemotherapy	Yes	No information	No information	No information
General anesthesia	Yes	No information	Yes (all received it)	No information

Risk of bias assessment (cohort-type studies)

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	N	Age, performance status, tumour size clinical stage, different lengths of follow-up among groups.
	If N or PN to 1.1:		
	1.2. Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding	Y	
	1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer questions 1.7 and 1.8, which relate to time-varying confounding	NA	
	If Y or PY to 1.2, or Y or PY to 1.3		

	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Y	Cox Multivariable regression analysis
	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	PY	
	1.6. Did the authors avoid adjusting for post-intervention variables?	Y	
	If N or PN to 1.2 and 1.3		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding?	PY	No mention of the time-varying confounding
	1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Y	
	Risk of bias judgement	Critical	Patients had a different prognosis in different groups. It was not clear from the report whether any patients switched among treatments. Some unknown confounders are not controlled for.
	Optional: What is the predicted direction of bias due to confounding?	Favours comparator	
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	N	Retrospective study, patients were selected according to the intervention they received.
	2.2. Do start of follow-up and start of intervention coincide for most subjects?	Y	
	2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	PN	Univariate regression to adjust for different baseline characteristics. The authors report that due to the high number of comparisons the reported p values are “purely descriptive” (no adjustment was made
	Risk of bias judgement	Serious	
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Unpredictable	
Bias in measurement of interventions	3.1 Is intervention status well defined?	PN	Different interventions are grouped under the same arm: Some patients received lymph node dissection, other not. 36% underwent video-assisted thoracoscopic surgery, and 64% underwent anatomical segmentectomy and 86% underwent wedge resection. 57% underwent SABR and 43% underwent CFRT. All patients who underwent focal ablation received bipolar RFA under general anesthesia.
	3.2 Was information on intervention status recorded at the time of intervention?	N	Retrospective study
	3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	PY	
	Risk of bias judgement	Serious	
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Unpredictable	
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups?	NI	No information is reported on whether patients had received chemotherapy.
	4.2. Were numbers of switches to other interventions low?	Y	Patients in the RT and RFA groups could not receive surgery.
	4.3. Was implementation failure minor?	NI	
	4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these issues?	NA	
	Risk of bias judgement	Serious	
	Optional: What is the predicted direction of bias due to departures from the intended interventions?	Unpredictable	

Bias due to missing data	5.1 Are outcome data reasonably complete?	Y	
	5.2 Was intervention status reasonably complete for those in whom it was sought?	Y	
	5.3 Are data reasonably complete for other variables in the analysis?	Y	
	5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA	
	5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	NA	
	Risk of bias judgement	Low	
Bias in measurement of outcomes	6.1 Was the outcome measure objective?	PY	
	6.2 Were outcome assessors unaware of the intervention received by study participants?	NI	
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	
	6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	NI	
	Risk of bias judgement	Critical	Retrospective study
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Unpredictable	
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	PN	
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Y	Multiple comparisons
	7.3 ... different *subgroups*?	N	
	Risk of bias judgement	Serious	The results presented were not interpretable, p values only indicative.
	Optional: What is the predicted direction of bias due to selection of the reported result?	Unpredictable	
Overall bias	**Risk of bias judgement**	Critical	
	Optional: What is the overall predicted direction of bias for this outcome?	Unpredictable	

Abbreviations: CFRT = conventional fractionation radiation therapy; N = no; NA = not applicable; NI = no information; PN = probably not; PY = probably yes; RFA = radiofrequency ablation; RT = radiation therapy; Y = yes

The ACROBAT-NRSI tool (2): For each study

Specify a target trial specific to the study.

Kwan et al., 2014 [21]

The protocol-specified target randomized trial fully applies	☐	*OR*	Participants	Patients 65years old or older with stage 1A or 1B nonsmall cell lung cancer
			Experimental intervention	Thermal ablation
			Control intervention	Sublobar resection

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Survival (overall survival, cancer-specific survival

Specify the effect of interest

E.g., effect of *initiating* intervention (as in an intention-to-treat analysis), or effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Effect of initiating the intervention.

Specify the specific result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g., RR = 1.52 (95% CI, 0.83 to 2.77) and/or a reference (e.g., to a table, figure or paragraph) that uniquely defines the result being assessed.

Table 3b

Preliminary consideration of confounders

a. Within each confounding domain listed in the review protocol, list the relevant variables, if any, measured in this study.

Bias due to confounding: E.g., performance status, tumour size, clinical stage. Follow-up times of different length.

Bias due to patients selection: Because of the nature of this population-based study, the authors could not control or know about the reasons why each patient was selected for a specific treatment.

b List additional confounding domains, if any, specific to the setting of this particular study. Within each domain, list the relevant variables, if any, measured in this study.

This study does not report enough details about the interventions to be able to detect any bias. It is about thermal ablation.

c List additional domains and corresponding measured variables, if any, that the study authors identified as potential confounders that are not included in the above domains.

Bias in measurement of outcomes: page 7: it is possible that statistical power to detect a difference may have been limited by the smaller size of the matched groups.
Bias in intervention measurement: The authors grouped several procedures together: wedge resection, segmentectomy, and approaches (video-assisted thoracosopic) under the category of subolbar resection and thermal ablation (do not specify whether it is radiofrequency or cryotherapy).
Since this is an observational study, unmeasured confounders are not accounted for in the attempt to control for bias.

Relationship between confounding domains and potential confounders.

In the table below, "critically important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Confounding domain	Is the domain critically important?*	Measured Variable	Did the authors demonstrate that controlling for this variable was unnecessary?*	Is the domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to move the effect estimate up or down? **
Bias due to confounding	Yes	Age	No (age was a significant predictor of OS). Older pts had worse survival HR range = 1.122-2.708, p<0.0001	Yes	Down (higher risk of cancer-specific death for RFA compared to surgery HR = 1.185, P = 0.026)
		Male sex	No (sex was a significant predictor of OS). Male had lower risk than female patients: HR = 0.667, p<0.0006		
		Cancer stage	No (cancer stage was a significant predictor of OS). Patients with stage 1B had worse survival tha patients with stage 1A HR = 1.277, p=0.037		

		Comorbidity index	Yes (results from multivariate model showed that co-morbidity had minimal impact on survival) (p=0.848)		
Bias due to pts selection	Yes	Demographic characteristics and comorbidity	No (statistically significant differences for sex, age cancer stage tumour histology were shown in the multivariate Cox model for OS and CSS)	Yes	Down (towards no difference between groups for OS)

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

** For example, if the crude effect estimate is 1.3, adjustment to 1.6 is up, while adjustment to 0.7 is down. If the effect estimate is 0.7, adjustment to 1.1 is up while adjustment to 0.4 is down.

Abbreviations: CSS = cancer-specific survival; HR = hazard ratio; OS = overal survival; RFA = radiofrequency ablation

Preliminary consideration of co-interventions

a. Are the (pre-specified) co-interventions likely to be administered in the context of this study?

Yes

b List additional co-interventions, if any, specific to the setting of this particular study.

None known – the authors controlled with the billing data and excluded patients who had co-interventions

Co-interventions

In the table below, "critically important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the variables fully measure the co-intervention, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Co-intervention	Is the co-intervention critically important?*	Did the authors demonstrate that controlling for this co-intervention was unnecessary?	Is the co-intervention measured validly and reliably?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
Receipt of adjuvant chemotherapy	Yes	Yes (no statistically significant difference between groups in OS and CSS, although chemotherapy time showed a difference)	Yes	No information
Received radiotherapy	Yes	Yes (no difference in the multivariate Cox regression for OS)	Yes	No information

Abbreviations: CSS = cancer-specific survival; OS = overal survival

Risk of bias assessment (cohort-type studies)

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	N	The authors controlled for some factors, but many unknown confounders can be present in a retrospective study. Patients had different prognosis at start.
	If N or PN to 1.1:		

	1.2. Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding	PY	Data from claim data
	1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer questions 1.7 and 1.8, which relate to time-varying confounding	NA	
	If Y or PY to 1.2, or Y or PY to 1.3		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Y	
	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Y	
	1.6. Did the authors avoid adjusting for post-intervention variables?	Y	
	If N or PN to 1.2 and 1.3		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding?	Y	
	1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Y	
	Risk of bias judgement	Moderate	Patients had different prognosis in different arms of the study
	Optional: What is the predicted direction of bias due to confounding?	Unpredictable	
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	N	Data from registry
	2.2. Do start of follow-up and start of intervention coincide for most subjects?	N	Data from registry
	2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y	Multivariate regression with propensity score matching
	Risk of bias judgement	Low	Authors appropriately controlled for selection bias, and they include a very large number of patients
Bias in measurement of interventions	3.1 Is intervention status well defined?	N	Authors included various intervention in each arm. In the thermal ablation it was mainly RFA, but in the surgery, wedge resection, video-assisted thoracoscopy and sublobar resection were pooled together.
	3.2 Was information on intervention status recorded at the time of intervention?	Y	Claim data and codes
	3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	Y	
	Risk of bias judgement	Moderate	
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups?	N	
	4.2. Were numbers of switches to other interventions low?	NI	
	4.3. Was implementation failure minor?	Y	
	4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these issues?	Y	
	Risk of bias judgement	Moderate	Data from claims
Bias due to missing data	5.1 Are outcome data reasonably complete?	Y	Claim data
	5.2 Was intervention status reasonably complete for those in whom it was sought?	Y	Claim data

	5.3 Are data reasonably complete for other variables in the analysis?	Y	
	5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA	
	5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	NA	
	Risk of bias judgement	Low	Retrospective study
Bias in measurement of outcomes	6.1 Was the outcome measure objective?	Y	
	6.2 Were outcome assessors unaware of the intervention received by study participants?	PN	
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	
	6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	NI	
	Risk of bias judgement	Moderate	
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Unpredictable	
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	Y	
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Y	
	7.3 ... different *subgroups*?	Y	
	Risk of bias judgement	Low	
Overall bias	**Risk of bias judgement**	Low	

Abbreviations: N = no; NA = not applicable; NI = no information; PN = probably not; PY = probably yes; RFA = radiofrequency ablation; Y = yes

The ACROBAT-NRSI tool (2): For each study

Specify a target trial specific to the study.

Alexander et al. 2013b [22]

The protocol-specified target randomized trial fully applies	☐	*OR*	Participants	Patients with stage IA or IB lung cancer
			Experimental intervention	Radiofrequency ablation
			Control intervention	Limited surgical resection

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Survival (overall survival cancer-specific survival

Specify the effect of interest

E.g., effect of *initiating* intervention (as in an intention-to-treat analysis), or effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Initiating the intervention

Specify the specific result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g., RR = 1.52 (95% CI, 0.83 to 2.77) and/or a reference (e.g., to a table, figure or paragraph) that uniquely defines the result being assessed.

Table 3b

Preliminary consideration of confounders

a. Within each confounding domain listed in the review protocol, list the relevant variables, if any, measured in this study.

Table 3b

b List additional confounding domains, if any, specific to the setting of this particular study. Within each domain, list the relevant variables, if any, measured in this study.

Small sample size

c List additional domains and corresponding measured variables, if any, that the study authors identified as potential confounders that are not included in the above domains.

Bias due to missing data (patients who moved away and lost to follow-up)

Relationship between confounding domains and potential confounders.

In the table below, "critically important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Confounding domain	Is the domain critically important?*	Measured Variable	Did the authors demonstrate that controlling for this variable was unnecessary?*	Is the domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to move the effect estimate up or down? **
Bias due to confounding	Yes	Age	No (pts in the surgery group were younger: RFA vs. surgery: (mean) 77.8 vs. 73.8 P=0.0123)	Yes	No information
		Other demographic	Yes (no statistically significant difference)		

Bias in selection of pts	Yes	None	NA	No	No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

** For example, if the crude effect estimate is 1.3, adjustment to 1.6 is up, while adjustment to 0.7 is down. If the effect estimate is 0.7, adjustment to 1.1 is up while adjustment to 0.4 is down.

Preliminary consideration of co-interventions

a. Are the (pre-specified) co-interventions likely to be administered in the context of this study?

Yes (Chemotherapy, radiotherapy)

b List additional co-interventions, if any, specific to the setting of this particular study.

Adjuvant therapy (brachytherapy)

Co-interventions

In the table below, "critically important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the variables fully measure the co-intervention, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Co-intervention	Is the co-intervention critically important?*	Did the authors demonstrate that controlling for this co-intervention was unnecessary?	Is the co-intervention measured validly and reliably?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
Adjuvant therapy	Yes	Yes (P = 0.7559)	No information	No information

Risk of bias assessment (cohort-type studies)

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	N	Retrospective study, pts population have different age, different prognosis.
	If N or PN to 1.1:		
	1.2. Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding	Y	
	1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer questions 1.7 and 1.8, which relate to time-varying confounding	NA	
	If Y or PY to 1.2, or Y or PY to 1.3		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Y	
	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Y	
	1.6. Did the authors avoid adjusting for post-intervention variables?	Y	

	If N or PN to 1.2 and 1.3		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding?	NA	
	1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA	
	Risk of bias judgement	Serious	
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	N	Retrospective study
	2.2. Do start of follow-up and start of intervention coincide for most subjects?	N	
	2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y	
	Risk of bias judgement	Moderate	
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Unpredictable	
Bias in measurement of interventions	3.1 Is intervention status well defined?	Y	
	3.2 Was information on intervention status recorded at the time of intervention?	Y	
	3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	N	
	Risk of bias judgement	Serious	
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Unpredictable	
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups?	PY	
	4.2. Were numbers of switches to other interventions low?	NI	
	4.3. Was implementation failure minor?	NI	
	4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these issues?	NA	
	Risk of bias judgement	Moderate	
	Optional: What is the predicted direction of bias due to departures from the intended interventions?	Unpredictable	
Bias due to missing data	5.1 Are outcome data reasonably complete?	N	
	5.2 Was intervention status reasonably complete for those in whom it was sought?	Y	
	5.3 Are data reasonably complete for other variables in the analysis?	Y	
	5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA	
	5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	NA	
	Risk of bias judgement	Moderate	
Bias in measurement of outcomes	6.1 Was the outcome measure objective?	Y	
	6.2 Were outcome assessors unaware of the intervention received by study participants?	PN	
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	
	6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	NI	

	Risk of bias judgement	Moderate	
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	PY	OS and CSS
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	N	
	7.3 ... different *subgroups*?	N	
	Risk of bias judgement	Moderate	
	Optional: What is the predicted direction of bias due to selection of the reported result?	Unpredictable	
Overall bias	**Risk of bias judgement**	Serious	

Abbreviations: CSS = cancer-specific survival; N = no; NA = not applicable; NI = no information; OS = overal survival; PN = probably not; PY = probably yes; RFA = radiofrequency ablation; Y = yes

The ACROBAT-NRSI tool (2): For each study

Specify a target trial specific to the study.

Matsui et al., 2012 [24]

The protocol-specified target randomized trial fully applies		*OR*	Participants	Patients with lung cancer
			Experimental intervention	Phrenic nerve injury after radiofrequency ablation
			Control intervention	No phrenic nerve injury after radiofrequency ablation

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Phrenic nerve injury

Specify the effect of interest

E.g., effect of *initiating* intervention (as in an intention-to-treat analysis), or effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Effect of initiating intervention

Specify the specific result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g., RR = 1.52 (95% CI, 0.83 to 2.77) and/or a reference (e.g., to a table, figure or paragraph) that uniquely defines the result being assessed.

Table 3b

Preliminary consideration of confounders

a. Within each confounding domain listed in the review protocol, list the relevant variables, if any, measured in this study.

Bias due to confounding: In cases when the phrenic nerve could not be identified with a computed tomography scan it was estimated by standard imaging atlas and error could have occurred.

Bias in selection: the authors recruited eight randomly sampled controls per case using a random number table

b List additional confounding domains, if any, specific to the setting of this particular study. Within each domain, list the relevant variables, if any, measured in this study.

Bias in measurement of intervention: the authors used two different systems for RFA

c List additional domains and corresponding measured variables, if any, that the study authors identified as potential confounders that are not included in the above domains.

Bias in measurement of outcome: Pleural effusion and pneumothorax may cause false positive results.

Relationship between confounding domains and potential confounders.

In the table below, "critically important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Confounding domain	Is the domain critically important?*	Measured Variable	Did the authors demonstrate that controlling for this variable was unnecessary?*	Is the domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to move the effect estimate up or down? **
Bias due to confounding	Yes	Tumour size	Yes (no statistically significant difference between cases and controls)	No: Number of cases where the position of the phrenic nerve was estimated by atlas was not recorded.	No information
		Tumour distance from phrenic nerve	No (tumours <10 mm closer to the phrenic nerve were more likely to result in injury, p<0.001)		
Bias in measurement of intervention	Yes	Radiofrequency electrode type	Yes: No statistically significant difference with different electrode types.	No: Number of false positive results was not recorded	No information
Bias in measurement of outcome	Yes	Not measured	No	No: not measured	No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

** For example, if the crude effect estimate is 1.3, adjustment to 1.6 is up, while adjustment to 0.7 is down. If the effect estimate is 0.7, adjustment to 1.1 is up while adjustment to 0.4 is down.

Preliminary consideration of co-interventions

a. Are the (pre-specified) co-interventions likely to be administered in the context of this study?

Yes 2 patients received general anesthesia.

Number of patients who had received adjuvant radiotherapy and chemotherapy were not recorded.

b List additional co-interventions, if any, specific to the setting of this particular study.

None

Co-interventions

In the table below, "critically important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the variables fully measure the co-intervention, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

Co-intervention	Is the co-intervention critically important?*	Did the authors demonstrate that controlling for this co-intervention was unnecessary?	Is the co-intervention measured validly and reliably?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
Adjuvant therapy	Yes	No: not discussed	No information	No information (could potentially create more cases)
General anesthesia	No	No: not discussed	No information	No information

Risk of bias assessment (case-control studies).

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	PN	
	If N or PN to 1.1:		
	1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Y	
	1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	PY	
	1.6. Did the authors avoid adjusting for post-intervention variables?	Y	
	Risk of bias judgement	Moderate	
Bias in selection of participants into the study	2.4 Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	N	Patients had different prognosis
	Risk of bias judgement	Critical	
Bias in measurement of interventions	3.1 Is intervention status well defined? 3.2 Was information on intervention status recorded at the time of intervention? 3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome? **Risk of bias judgement** Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	PN Y Y Critical Unpredictable	The authors used two different RFA systems, retrospectively collected data
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups? 4.2. Were numbers of switches to other interventions low? 4.3. Was implementation failure minor? **Risk of bias judgement**	NI Y Y Moderate	

	Optional: What is the predicted direction of bias due to departures from the intended interventions?	Unpredictable	
Bias due to missing data	5.1 Was outcome status reasonably complete for those in whom it was sought? 5.2 Were data on intervention status reasonably complete? 5.3 Are data reasonably complete for other variables in the analysis? 5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across cases and controls? 5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data? **Risk of bias judgement**	Y Y N NI N Moderate	
Bias in measurement of outcomes	6.1 Was the definition of case status (and control status, if applicable) based on objective criteria? 6.2 Was the definition of case status (and control status, if applicable) applied without knowledge of the intervention received? **Risk of bias judgement** Optional: What is the predicted direction of bias due to definitions of case and control status?	PY NI Serious Unpredictable	
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from... 7.1. ... multiple *definitions of the intervention*? 7.2 ... multiple *analyses* of the intervention-outcome relationship? 7.3 ... different *subgroups*? **Risk of bias judgement**	 N N N Moderate	
Overall bias	**Risk of bias judgement**	Critical	

Abbreviations: N = no; NA = not applicable; NI = no information; OS = overal survival; PN = probably not; PY = probably yes; RFA = radiofrequency ablation; Y = yes

Appendix 6:

Table 1a. Noncomparative studies of radiofrequency ablation: General characteristics

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
Studies of Primary Lung Cancer				
Dupuy, 2015 [25], Z4033 **Country**: US **Funding**: National Institutes of Health and Valleylab (Covidien) Boulder, CO.	**Design:** Case series for OS and local control Before-after for pulmonary function (prospective, multicentre) **Data collection:** Dec 2006 –Nov 2010 **Follow-up:** 24 mos	N=51 inoperable pts with Stage IA NSCLC **Lesion size:** ≤3 cm **Sex:** Men 45% **Age:** (median) 76 yrs; range, 60 to 89 yrs	CT-guided percutaneous RFA **Device:** Covidien cluster Cool-tip electrode (Covidien, Boulder, CO, US) **Target temperature**: ≥60˚C. **Procedure**: At least 1 treatment with the maximal allowable current for no more than 12 min at a single position. Max energy delivery per tumour: 36 min. Details on anesthesia: NR **Operator experience:** Physicians had to have performed 25 static or dynamic image-guided thoracic procedures as well as 10 lung RFA ablation procedures (at least 1 with the Covidien system)	OS AE Local control Pulmonary function (FEV_1, diffusing capacity of lung for carbon monoxide)
Hassan, 2014 [26] **ABS** **Country**: Bangladesh **Funding**: NR	**Design:** Case series **Data collection:** 2000 to 2013 **Follow-up:** (median) 23.5 mos	N=130 pts with stage I NSCLC (subset of a larger sample [500 pts] including also pts with stage II and III disease). **Lesion size:** NR **Sex:** NR **Age:** NR	RFA + RT **Device:** NR **Target temperature**: NR **Procedure**: NR **Operator experience:** NR	OS Local recurrence
Kodama, 2014 [27] **Country**: Japan **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Aug 2004 to May 2012 **Follow-up:** **(**mean): 42 ± 23 mos (range,5 to 92 mos)	33 pts with 42 lung tumours with ≥50% ground glass opacity. **Lesion size:** mean: 1.6 cm ± 0.9; range, 0.7 to 4 cm. **Sex:** Men 42.4% **Age** (mean)**:** 71.1 yrs, range, 46–84 yrs;	RFA **Device:** Cool-tip RFA system; Covidien, Boulder, CO, US **Target temperature**: NR **Procedure**: For analgesia: Fentanyl citrate (Fentanest; Daiichi Sankyo Co Ltd, Tokyo, Japan); for local anesthesia Lidocaine (Xylocaine; Astellas Pharma Inc, Tokyo, Japan). For tumours ≤2 cm, the electrode was placed in the centre of the tumour; for tumours >2 cm the electrode was placed sequentially at 2 or 3 different locations. Energy was applied with 20 W power, which was increased in increments of 10 W at 1 min interval for a time of 12 min per tumour.	Tumour progression OS AE

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
			Operator experience: 3 interventional radiologists with 22, 20, and 10 yrs of experience in oncologic interventional radiology under moderate sedation and local anesthesia with inpatients.	
Ridge, 2013 [28] **ABS** **Country**: NR **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** May 2006 to Sept 2010 **Follow-up:** 21 mos	N=31 pts with 23 T1a and 9 T1b primary lung tumours **Lesion size:** (median) 15 mm, range 8 to 30 mm **Sex:** Men 39% **Age:** (median) 74 yrs, range: 51 to 92	RFA **Device:** NR **Target temperature**: NR **Procedure**: NR **Operator experience:** NR	Local recurrence OS DFS AE
Lanuti, 2012 [29,87]** **Country**: US **Funding**: Division of Thoracic Surgery and Thoracic Radiology at the Massachusetts General Hospital	**Design:** Case series (retrospective) **Data collection:** 2003 to 2010 Jul 2003 to Feb 2008 [87] **Follow-up:**32 mos, range 2 to 75.2 mos; (median) 17.3±11 mos [87]	N=45 pts with stage I (T1 to T2a N0M0) NSCLC; N=31 pts with 34 inoperable stage I NSCLC [87] **Lesion size:** 2.0±1.0 cm (range, 0.7 to 4.5 cm). 2±1 cm, range 0.8 to 4.4 cm [87] **Sex:** Men 40% (45% [87]) **Age:** (median) 70 yrs [87]	RFA (55, and 38 [87] ablations) **Device**: Single or cluster (for lesions >1 cm) cool-tip electrode coupled to a generator and perfusion pump (Covidien, Valley Lab Division, Boulder, CO, US). **Target temperature**: >60°C (usually 90°C). **Procedure**: Conscious sedation with local analgesia (although some pts received general anesthesia). RFA procedure lasted 12 min. **Operator experience:** NR	Locoregional recurrence AE (pneumothorax) OS DFS 30-d mortality [87] Local progression [87] OS [87] DFS [87]
Ambrogi, 2011 [30] **Country**: Italy **Funding**: Italian Ministry of University and Research	**Design:** Case series **Data collection:** 2001 to 2008 **Follow-up:** (mean) 47 mos, (median) 45.5, range 12 to 82 mos	N=57 pts with 59 stage IA (n=44) and stage IB (n=15) NSCLC **Lesion size:** 2.6 cm, range, 1.1 to 5 cm **Sex:** Men 79% **Age:** 74 yrs; range, 40 to 88 yrs	RFA (80 ablations) **Device:** Radiofrequency generator: RITA Model 1500 and 1500X, (AngioDynamics, Latham, NY, US), and from 2007 StarBurst Talon, (AngioDynamics) with a perfusion system (Intelliflow pump, AngioDynamics) with a 14-gauge needle cannula with 9 deployable electrodes that open flower-like up to 5 cm. **Target temperature**: 90°C maintained from 15 to 27 min, and 105°C, maintained for 5 to 9 min. **Procedure**: Pts were under conscious sedation (ketorolac 0.5–0.8 mg/kg, propofol 1–2 mg/kg/h, and remifentanil 0.1 mg/kg/min) and treated with local analgesia (1% lidocaine). **Operator experience:** NR	AE CR Local recurrence interval OS CSS DFI

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
Hiraki, 2011 [31] **Country**: Japan **Funding**: None	**Design:** Case series **Data collection:** Jul 2002 to Sept 2009 **Follow-up:** (median) 37 mos, (mean) 39 mos, range 2 to 88 mos	N=50 pts with nonoperable stage IA (n=38) and IB (n=12) NSCLC (52 tumours) **Lesion size:** (mean) 2.1 cm, median 1.8 cm, range 0.7 to 6 cm **Sex:** Men 58% **Age:** (mean) 74.7 yrs; range, 52 to 88 yrs	Percutaneous RFA 52 sessions **Device**: RFA generator (Asteion; Toshiba, Tokyo, Japan) and multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA), a single internally cooled electrode (Cool-tip; Valleylab, Boulder, CO), or a cluster internally cooled electrode (n ¼ 2) (Cool-tip; Valleylab). RFA energy was applied for 12 min. **Target temperature**: ≥60°C for 15 min **Procedure**: Pts were treated with local analgesia or epidural anesthesia (15 sessions) and conscious sedation (0.3 mg fentanyl i.v. and 25 mg hydroxyzine i.m.). **Operator experience:** NR	AE Local efficacy OS CSS DFS
Beland, 2010 [32] **Country**: USA **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Jan 1998 to Jan 2008 **Follow-up:** (mean) 16 mos, range 1 to 72 mos	N=79 pts with 79 primary NSCLC. 71% stage IA, 16% stage IB, 4% stage IIB, 1% stage IIIA, 4% stage IIIB and 4% stage IV. **Lesion size:** 2.4 cm, range 1.1 to 5.5 cm **Sex:** Pts with recurrence: 47% men **Age:** 75 yrs; range, 45 to 91 yrs	RFA (24% pts underwent adjuvant external beam radiation and 11% concomitant brachytherapy) **Device:** A ML-1 generator (Covidien, Valley Lab Division, Boulder, CO, US) and a single or cluster Cool-tip electrode. **Target temperature**: >60°C or a sustained temperature of 55°C over >1 measurement. **Procedure**: Choice of the electrode was at the discretion of the operator. **Operator experience:** 92% [73 of 79] of the sessions were performed by three radiologists who had 5 to 12 yrs of experience using RFA.	Frequency and TTR DFS Factors associated with recurrence
Studies of Lung Metastases				
Ferguson, 2015 [33] **Country**: Australia **Funding**: No funding	**Design:** Case series (data collected prospectively and analyzed retrospectively) **Data collection:** 2000 to 2013 **Follow-up:** 28 mos	N=157 pts with colorectal lung metastases (434 lesion ablated in 199 procedures). Lesions with major venous, bronchus or hilar involvement were excluded. **Lesion size:** (mean) 3.82 cm **Sex:** Men 54% **Age:** (mean) 64 yrs; range, 28 to 86 yrs	RFA **Device:** NR **Target temperature**: NR **Procedure**: NR **Operator experience:** NR	OS DFS Procedure-related mortality and morbidity Prognostic factors for survival.
Wang, 2015 [34] **Country**: China **Funding**: NR	**Design:** Case series **Data collection:** Jan 2008 to Oct 2014	N=35 pts with 67 residual lung metastases from breast cancer after chemotherapy with 1 to 3 lesions after chemotherapy, performance	RFA **Device:** A radiofrequency generator (CelonLab POWER, OLYMPUS), Cold Circulation Pump (Celon Aquaflow ¢Û, OLYMPUS), and a radiofrequency needle electrode (OLYMPUS CelonproSurge: T20, T30, T40, i.e., 2, 3, and 4 cm and the maximum output power 20W, 30W, 40W respectively). **Target temperature**: NR	Local control OS AE (treatment-related)

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
	Follow-up: NR	status 0-1, and life expectancy ≥3 mos. **Lesion size:** ≤2 cm 39 lesions (20 pts); >2cm 28 lesions (15 pts) **Sex:** all women **Age:** >65 yrs: 17%; ≤65 yrs: 83%	**Procedure**: Ablation finished when ground-glass opacity was 0.5–1 cm away from the tumour boundary. **Operator experience:** NR	
Matsui, 2015 [35] **Country**: Japan **Funding**: NR	**Design:** Case series **Data collection: Jun 2001 to Dec 2012** **Follow-up:** 37.5 mos	N=84 pts with colorectal lung metastases with 172 metastases **Lesion size:** (median) 1.2 cm **Sex:** Men 55% **Age:** (median) 65 yrs; range, 31 to 94 yrs	RFA **Device:** A RF generator (RF 2000 or RF 3000 [Boston Scientific] or CC-1 [Covidien]), and a multitined expandable electrode (Le Veen; Boston Scientific, Natick, MA) (93 sessions, and a single internally cooled electrode (Cool-tip; Covidien, Mansfield, MA) (20 sessions) **Target temperature**: Temperature was maintained for 15 min when using the RF 2000 and RF 3000 generator; for 12 min with the CC-1 generator. **Procedure**: Performed on inpatients. The ablation aimed at the tumour and 5 mm of parenchyma. **Operator experience:** NR	OS Local tumour progression Factors associated with improved survival AE
Gillams, 2013 [36] **Country**: UK **Funding**: NR	**Design:** Case series **Data collection:** 2002 to 2011 **Follow-up: NR**	N=122 pts with 398 colorectal cancer lung metastases **Lesion size:** 1.7 cm (range, 0.5 to 4) **Sex:** Men 71.3% **Age:** (median) 68 yrs; range, 29 to 90 yrs	Percutaneous RFA (256 procedures) **Device:** A 200 W generator (Covidien Healthcare, Boulder, CO, USA), and 1,2, or 3 single electrodes depending of the tumour size. **Target temperature**: Ablation was performed at a maximum power of <100 W or, in pts under conscious sedation, at maximum power consistent with pt tolerance. The temperature was between 60 and 70°C maintained for up to 5 min. **Procedure**: Pts were under conscious sedation or general anesthesia (numbers not given). Ablation was aimed to achieve a min of 5 mm ground glass opacity around the tumour. **Operator experience:** NR	OS AE
Petre, 2013 [37] **Country**: US **Funding**: NR	**Design:** Case series **Data collection:** Dec 2004 to Jun 2010 **Follow-up:** 18 mos	N=45 pts with 69 colorectal cancer lung metastases not suitable for surgery. **Lesion size:** range: 0.4 to 3.5 cm. **Sex:** Men 64% **Age:** (median) 63 yrs; range, 43 to 81 yrs	RFA **Device:** One of 3 systems was used: the Cool-tip system (Covidien, Boulder, CO,US), the RITA system (Angio-Dynamics, Queensbury, NY, US), or the LeVeen System (Boston Scientific, Natick, MA, US). **Target temperature**: Energy was delivered starting at 35 W and it was slowly increased over time. **Procedure**: The procedure varied according with the system used. **Operator experience:** NR	OS Local tumour progression-free survival
Hiraki, 2011b [38] **Country**: Japan **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** NR	N=32 pts with 83 pulmonary metastases from hepatocellular carcinoma	Percutaneous RFA (65 sessions) **Device:** multitined expandable electrodes with arrays 2 cm (LeVeen; Boston Scientific, Natick, MA, US) and a single internally cooled electrode with noninsulated tips (Cool-tip; Covidien, Mansfield, MA,US).	Technical effectiveness (eradication) Successful repeat ablation

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
	Follow-up: 20.5 mos	**Lesion size:** (median) 1.1cm; (mean): 1.1 cm, range 0.3 to 3.9 cm **Sex:** Men 75% **Age:** (mean) 61.9 yrs; range, 35 to 82 yrs	**Target temperature**: Energy was applied using an impedance control algorithm for 10–12 min during internal cooling of the electrode. When multitined-electrode devices, were used, initial RF power was set at 10–40 W and increased by 5-10 W every 1-2 min until impedance showed rapid increase or an automatic shutoff after 15 min. **Procedure**: Pts were under conscious sedation and local anesthesia alone (n=51) or a combination of local and epidural anesthesia (n=14). **Operator experience:** NR	AE OS Prognostic factors
Von Meyenfeldt, 2011 [39] **Country**: The Netherlands **Funding**: NR	**Design:** Case series **Data collection:** 2004 to 2009 **Follow-up:** (median) 22 mos, range, 2 to 65 mos	N=46 pts with 90 pulmonary metastases **Lesion size:** <2 cm 69% 2-3 cm 16% 3-5 cm 9% < 5 cm 6% **Sex:** Men 41% **Age:** (median) 57 yrs; range, 32 to 78 yrs	Percutaneous RFA (65 sessions) **Device: A** Radio Therapeutics RF generator (RF 3000, Radio Therapeutics Corporation, Sunnyvale, CA), and the Cool-tip RF Tissue Ablation System (Covidien, Boulder, CO, US) were used. **Target temperature**: NR **Procedure**: Pts had epidural anesthesia with conscious sedation. Ablation was performed according to the manufacturer's algorithms, and ablation time varied between 12 and 25 min. **Operator experience:** 2 experienced interventional radiologists.	AE Tumour progression OS PFS
Soga, 2009 [40] **Country**: Japan **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Jul 2001 to Jun 2008 **Follow-up:** 25 mos	N=39 pts with 135 unresectable lung metastases from RCC **Lesion size:** Curative RFA: 2.2±1.4 cm , range 0.6 to 5.8 Palliative RFA: 2.5±1.5, range e0.5 to 6.8 **Sex:** Men 79.5% **Age:** yrs; range, yrs	RFA used with curative intent (n=15); RFA used with palliative intent (n=24) **Device:** A generator (Series CC-1, Valleylab; RF3000, Boston Scientific, MA, US), with an internally cooled electrode (Cool-Tip RF Ablation System, Valleylab, Boulder, CO, US), or a multi-tined expandable electrode (Radiotherapeutic RF Ablation System, Boston Scientific Corp., Natick, MA, US) were used depending on the institution. **Target temperature**: Energy was applied for 10-12 min to each tumour **Procedure**: Performed on inpatients. Moderate sedation (Fentanyl citrate [Phentanest, Daiichi-Sankyo Pharmaceutical Co. Ltd, Tokyo, Japan] at a dose of 0.1–0.2 mg) and local anesthesia (Lidocaine [Xylocaine, Astellas Pharmaceutical Co. Ltd, Tokyo, Japan]) were used for analgesia. **Operator experience:** 5 radiologists performed the procedure.	OS AE Local progression RFS Prognostic factors
Yamakado, 2009 [41] **Country**: Japan **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Feb 2002 to Jul 2008 **Follow-up:** (mean) 24.6±17.6 (SD)	N=78 pts with 198 colorectal lung metastases **Lesion size:** 2.0±1.0 cm, range 0.6 to 6 cm **Sex:** Men 67.9% **Age:** (mean) 66.1±9.8 yrs; range, 40 to 87 yrs	RFA (140 sessions) **Device:** An internally cooled electrode (Cool-Tip RF Ablation System; Valleylab, Boulder, CO) was used. **Target temperature:** Energy was applied for 12 min at each tumour site. **Procedure**: Performed on inpatients. Moderate sedation (Fentanyl citrate [Phentanest, Daiichi-Sankyo Pharmaceutical Co. Ltd, Tokyo, Japan]) at a dose of 0.1–0.2 mg and local anesthesia (Lidocaine [Xylocaine, Astellas Pharmaceutical Co. Ltd, Tokyo, Japan]) were used for analgesia. **Operator experience**: 3 radiologists performed the procedure.	AE Local progression OS DFI Prognostic factors

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
	mos, range 6.0 to 84.1 mos			
Studies of Primary Lung Cancer and Lung Metastases, or not specified				
Akhan, 2016 [42] **Country:** Turkey **Funding:** NR	**Design:** Case series **Data collection:** Jun 2005 to Oct 2013. **Follow-up**: 27 mos	N=49 pts (20% primary and 80% metastatic) for a total of 112 tumours (10% primary nonsmall cell lung cancer and 90% metastatic) **Lesion size:** 0.6 to 4 cm (median 1.5 cm). **Sex:** Men 61% **Age:** 63 yrs; range, 13–85 yrs	CT-guided RFA (122 sessions) **Device:** Either the RITA (RITA Medical Systems, AngioDynamics) or the Cool-tip (Covidien) systems powered by 200 W or 250 W generators were used, with a 17-gauge multitined expandable electrode (The RITA StarBurst Talon or StarBurst Talon Semi-Flex RF ablation electrodes) **Target temperature**: 80˚C for 5 min if tumour diameter was 3 cm or for 9 min if their tumour was 4 cm **Procedure**: Pts were under conscious sedation (midazolam and fentanyl). **Operator experience:** NR	Success rate: primary and after re-treatment Tumour progression OS RFS AE
Kodama, 2015 [43] **Country**: Japan **Funding**: NR	**Design:** Case series (prospective) **Data collection:** Sept 2009 to Jul 2011 **Follow-up:** 22 mos	N=33 pts with tumours treated with 35 sessions with ≥2 months of life expectancy and performance status of 0 or 1. Primary (52%) or metastases (48%) **Lesion size:** 3.0±0.7 cm, range 2.0 to 4.4 cm **Sex:** Men 79% **Age:** (mean) 70.5±10 SD yrs; range, 46 to 87 yrs	RFA with a multiple-electrode switching system **Device**: A 17-gauge internally cooled electrode (Cool-Tip RFA System; Covidien, Boulder, CO, US) **Target temperature**: Energy was applied until the impedance of each site increased 30 Ω above the baseline level. **Procedure**: Pts were under moderate sedation; (Fentanyl citrate [Phentanest, Daiichi-Sankyo Pharmaceutical Co. Ltd, Tokyo, Japan]) and local anesthesia (Lidocaine [Xylocaine, Astellas Pharmaceutical Co. Ltd, Tokyo, Japan]) were used for analgesia. **Operator experience:** 3 radiologists with 22, 20, and 10 yrs of experience in oncologic interventional radiology performed the interventions.	AE Tumour progression
Garetto, 2014 [44] **Country**: Italy **Funding**: NR	**Design:** Case series **Data collection:** 2002 to 2011 **Follow-up:** (mean) 23 mos	N=81 pts (100 lesions): NSCLC (n=30) and metastases (n=70) **Lesion size:** (mean) 2.3 cm, median: 2 cm, range 0.8 to 8 cm **Sex:** Men 75% **Age:** (mean) 61.7 yrs, (median): 66 yrs; range, 17 to 88 yrs	Percutaneous RFA **Device:** The RITA (RITA Medical Systems, USA) (15/100 cases), LeVeen (Boston Scientific Corporation, USA) (75/100) and Meditalia (Meditalia Biomedica, Italy) systems with expandable needles were used. Generators used had a max power of 200 W. **Target temperature**: NR **Procedure**: Pts were under conscious sedation, and 10 ml of lidocaine hydrochloride 2% was used for local anesthesia. **Operator experience:** NR	CA Difference in diameter of lesions achieving CA and PA. Factors predictive of CA Recurrence TTP OS Predictors of survival at 3 yrs AE
Alexander, 2013a [45] **Country**: US	**Design:** Case series (retrospective) **Data collection:**	N=163 pts with 195 inoperable primary lung neoplasms (n=131) or lung metastases (n=32) that did	RFA or MWA[c] (216 sessions). 113 tumours were treated with RFA alone; 74 with MWA alone and 8 with both MWA and RFA in separate sessions. **Device:** A 200-W generator under impedance control (Cosman Coagulator-1; Covidien / Valleylab, Boulder, CO, US) with an internally cooled cluster	Rib fractures incidence Distance from peripheral border

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
Funding: Perfint and/or Biocompatibles, NeuWave Medical, BSD Medical (some of the authors)	Feb 2004 to Apr 2010 **Follow-up:** 20±15.2 (SD) mos	not involve the osseous structures of the chest. **Lesion size:** 2.56 cm (range, 0.6 to 7.6 cm); Distance from chest wall (mean): 1.24 cm **Sex:** Men 52% **Age:** (mean) 73 yrs; range, 42 to 94 yrs	radiofrequency electrode (2.5-cm active tip) or a single-tip applicator (1–3-cm active tip) for RFA. A microwave generator (Viva-Wave Microwave Coagulation System; Covidien/Valleylab) (60 W power and a frequency of 915 MHz) and 3 applicators: a 14.5-gauge straight microwave antenna at 45 W, a 14.5-gauge straight microwave antenna at 50 or 60 W, and a multitine deployable ring (Viva Tri; Covidien/Valleylab) at 60 W. **Target temperature**: NR **Procedure**: Pts were under conscious sedation (fentanyl and midazolam). The decision to use RFA or MWA was based on operator preference, patient preference, tumour location, and tumour size, with peripheral and smaller lesions usually treated with RFA. **Operator experience:** 11 interventional radiologists, who had between 3 and 19 yrs of ablation experience.	of the ablation zone to the fractures rib. Factors predictors of fracture.
Galbis Caravajal, 2013 [46] **Country**: Spain **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** NR **Follow-up:** NR	N=59 pts (70 procedures) non-surgical candidates (36 pts with primary lung cancer and 23 pts with metastases)[d] **Lesion size:** 2.63±1.19 (SD) cm **Sex:** Men 95% **Age:** (mean) 71.08 yrs; (median) 72 yrs, range, 43 to 87 yrs	RFA **Device:** NR **Target temperature**: NR **Procedure**: Pts received conscious sedation. **Operator experience:** NR	OS AE
Baodong, 2011 [47] **ABS** **Country**: China **Funding**: NR	**Design:** Case series **Data collection:** NR **Follow-up:** NR	N=100 pts with lung cancer (106 lesions): 86 pts had primary lung cancer, 14 had metastases[e]. **Lesion size:** NR **Sex:** Men 62% **Age:** 66.6 yrs; range, 36 to 91 yrs	RFA **Device:** NR **Target temperature**: NR **Procedure**: NR **Operator experience:** NR	OS
Huang, 2011 [48] **Country**: China **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Oct 1999 to Jul 2006 **Follow-up:** (median) 24 mos	N=329 pts with primary NSCLC (n = 237) and lung metastases (n = 92), **Lesion size:** <3 cm: 253 tumours ≥3 cm and ≤4 cm: 102 tumours ≥4 cm: 81 tumours	RFA: 436 nodules treated **Device:** A 50 or 90 W radiofrequency generator with an expandable needle with seven or nine **Target temperature**: **Procedure**: the point of the needle was inserted into the deepest part of the tumour and the tines were deployed once every 2 cm. **Operator experience:** NR	AE Local progression PFI OS

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
		Sex: Men 63% **Age:** 62.1±7.8 (SD) yrs; range, 20 to 82 yrs		
Kashima, 2011 [49] **Country**: Japan **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Feb 2002 to Mar 2010 **Follow-up:** 22.1±17.9 mos, range, 3 to 84 mos	N=420 pts with 1403 lung tumours: 33% (137) had primary lung cancer and 67% (283) had metastases **Lesion size:** 1.8±1.3 cm, range 0.3 to 6 cm **Sex:** Men 60.2% **Age:** (mean) 63±14.6 (SD) yrs; range, 3 to 87 yrs	RFA (1000 sessions) **Device:** A generator (series CC-1–100, Valleylab) and internally cooled RFA electrodes (Cool-tip, Valleylab) **Target temperature**: Energy was applied for 10–12 min at each site. **Procedure**: Performed on inpatients. Pts received conscious sedation and local anesthesia Fentanyl citrate 0.1–0.2 mg (Fentanest, Janssen-Kyowa) and lidocaine hydrochloride 0.5% or 1% (Xylocaine Polyamp, AstraZeneca PLC) . **Operator experience:** 3 experienced interventional radiologists performed the interventions.	AE Risk factors for AE
Nour-Eldin, 2011 [50] **Country**: Germany **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Mar 2004 to Jan 2009 **Follow-up:** NR	N=164 pts with 20 primary lung tumours and 228 metastatic lesions **Lesion size:** NR **Sex:** Men 56.1% **Age:** mean 59.7±10.2 yrs	RFA (248 sessions) **Device:** A Celon Pro Surge bipolar internally cooled 15 gauge applicator and the Celon POWER System, (Celon AG Medical Instruments, Teltow, Germany) (power: 5–25 W; mean ablation time: 20 min ±10); or the 14-gauge RITA®Starburs TM XL and a RITA RF Generator (RITA Medical Systems, Inc., Manchester, GA). Mean ablation time: 25±7.5 min. **Target temperature**: 95–100°C **Procedure**: Pts received conscious sedation and local analgesia (fentanyl citrate 1 µg/kg and midazolam hydrochloride 0.010–0.035 mg/kg) **Operator experience:** 2 interventional radiologists with 8 and 15+ yrs experience	Mortality Incidence of pulmonary hemorrhage Risk factors for pulmonary hemorrhage
Hiraki, 2010 [51] **Country**: Japan **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Oct 2003 to Dec 2007 **Follow-up:** 15.9±8.5 mos	N=105 pts with 252 primary lung cancer (n=35 tumours in 32 pts) and lung metastases from CRC (n=117 tumours in 40 pts), lung cancer (n=23 in 13 pts), RCC (n= 49 in 7 pts), HCC (n=28 in 13 pts). **Lesion size:** mean 13.5±7.1 mm **Sex:** Men 70% **Age:** mean 66.6±11.4 yrs	RFA **Device:** A generator (RF 2000 or RF 3000; Boston Scientific, MA, US) and a multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA, US) **Target temperature**: energy was applied until a rapid increase in the impedance occurred or automatic shut-off at 15 min. Temperature NR. **Procedure**: Pts received local anesthesia and i.v. fentanyl or epidural anesthesia. **Operator experience:** NR	Local control
Chua, 2010 [52,88] **Country**: Australia	**Design:** Case series (prospective) **Data collection:** From Nov 2000 (ongoing)	N=148 pts with primary NSCLC and lung metastases **Lesion size:** 4±1 (SD) cm **Sex:** Men 56%	Percutaneous RFA (188 ablations) **Device:** A Rita 1500 generator (Rita Medical, Mountain View, CA) with a 14-gauge Rita Starburst XL probe. **Target temperature**: 90°C. The temperature was maintained for 15, 20, and 37 min for lesions of 3, 4, and 5 cm respectively.	CR PR Stable Disease PD OS

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
Funding: NR	**Follow-up:** 29 mos, range 2 to 103 **Subgroup** **Follow-up:** (median) 23 mos, range 1 to 96 mos	**Age:** (median) 63 yrs; range, 30 to 85 yrs **Subgroup** Published in Chua 2010b [88] (case series, retrospective) : 100 pts with colorectal lung metastases **Sex:** Men 61% **Age:** 65±11 (SD) yrs	**Procedure**: Pts were under light sedation and received i.v. midazolam and local anesthetic (Xylocaine 1%) **Operator experience:** NR	Predictors of survival AE LOS **Subgroup** OS Predictors of OS
Steinke, 2010 [53] **ABS** **Country**: Australia **Funding**: NR	**Design:** Case series **Data collection:** NR **Follow-up:** NR	N=100 pts with primary and metastatic lung cancer **Lesion size:** 3.5 cm **Sex:** NR **Age:** NR	RFA **Device:** NR **Target temperature**: NR **Procedure**: NR **Operator experience:** NR	Technical problems AE
Bozzi,, 2009 [54] **ABS** **Country**:Italy **Funding**: NR	**Design:** Case series **Data collection:** NR **Follow-up: NR**	N=114 pts with 137 tumours **Lesion size:** mean 2.3±1 cm (range, 0.7 to 7 cm) **Sex:** NR **Age:** NR	Percutaneous RFA **Device:** A 150-200 W generators and multitined expandable electrodes **Target temperature**: NR **Procedure**: Pts received conscious sedation **Operator experience:** NR	AE
Zhu, 2009 [55] **Country**: Australia **Funding**: NR	**Design:** Case series (retrospective) **Data collection:** Nov 2000 **Follow-up:** NR	N=100 pts with primary (n=6) and secondary (n=94) lung tumours **Lesion size:** (mean) 1.9±1.2 cm; (median) 2.0 cm, range 0.5 to 5 cm **Sex:** Men 56% **Age:** (mean) 65±8 yrs	Percutaneous RFA (129 sessions) **Device:** A RITA 1500 generator (RITA Medical Mountain View, CA, US) with a 14 gauge RITA starburst XL electrode probe and multitined expandable electrodes. **Target temperature**: The temperature of 90°C with a max power of 150 W was maintained for 15, 20, and 27 min for ablation zones of 3, 4, and 5 cm respectively. **Procedure**: Pts received the first 100 ablations under conscious sedation and local anesthesia (i.v. Morphine and Midazolam and Lignocaine 1). Pts in the subsequent 29 ablations received general anesthesia and positive pressure ventilation through endotracheal intubation. **Operator experience:** Procedures were performed by 2 interventional radiologists	Incidence and risk factors of AE LOS

**There is overlap between the 2012 and 2009 publications.
[a] Not attributable to RFA.
[b] Calculated from the first RFA treatment.
[c] Peripheral lesions close to or involving the pleura were usually treated with RFA; larger lesions, or in cases of recurrence near a heat sink were usually treated with MWA.
[d] This study included 32 pts with stage I lung cancer, 23 cases of pts with metastases, and 4 pts other stages of lung cancer.
[e] The number of pts with early stage is not reported.

Abbreviations: ABS = abstract; AE = adverse events; CA = complete ablation; CR = complete response; CRC = colorectal cancer; CSS = cancer-specific survival; CT = computed tomography; DFI = disease-free interval; DFS = disease-free survival; ds = days; FEV_1 = forced expiratory volume in the first second of expiration; HR = hazard ratio; HCC = hepatocellular carcinoma; im = intramuscular; iv intravenous; LOS = length of hospital stay; max = maximum; min = minute; mos = months; MWA = microwave ablation; N = sample

size; NA = not applicable; NR = not reported; NSCLC = non small cell lung cancer; OS = overall survival; PA = partial ablation; PD = progressive disease; PFI = progression-free interval; PFS = progression-free survival; PR = partial response; pts = patients; RCC = renal cell carcinoma; RF = rdiofrequency; RFS = recurrence-free survival; RT = radiotherapy; SD = standard deviation; TTP = time to progression; TTR = time to recurrence; yrs = years

Table 1b. Noncomparative studies of radiofrequency ablation: Summary results.

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Studies of Primary Lung Cancer						
Dupuy, 2015 [25], Z4033	**OS rates:** At 1 yr: 86.3%, 95% CI: 77.3% to 96.3% At 2 yrs: 69.8%, 95% CI: 58.0% to 83.9% Pulmonary function at 3 and 24 mos: NS difference in FEV_1 or D_{LCO} after RFA. When compared to baseline, FEV_1 at 3 and 24 mos was improved P=0.02 and p<0.01.	NR	NR	RFS rates: At 1 yr: 68.9%, 95% CI: 57.0% to 83.4% At 2 yrs: 59.8%, 95% CI: 47.2% to75.7%	**Subgroups:** **Tumour Size** Tumour size <2cm and performance status of 0 or 1 were associated with improved OS of 83% and 78% at 2 yrs (statistically significant). No statistically significant difference was noted for RFS.	**AE:** During the first 90 ds after RFA: In 12 pts Grade 3: 21 Grade 4: 2[a] Grade 5: 1[a]
Hassan, 2014 [26] ABS	**OS rates**: At 1 yr: 96% At 2 yrs: 87% At 3 yrs: 78% At 4 yrs: 67%	NR	NR	Local recurrence (tumours <5 cm): At 1 yr: 2.8%	NR	**AE:** 1n 500 pts Pneumothorax: 19, Infections: 35
Kodama, 2014 [27]	**OS rates**: At 1 yr: 100% At 3 yrs: 96.4% (95%CI, 77.5% to 99.5%) At 5 yrs: 96.4% (95%CI, 77.5% to 99.5%)	NR	NR	**Tumour progression:** Tumour recurrence rate: 30.3% Distant metastases: 12.1% Local tumour progression rate: At 1 yr: 0% At 3 yrs: 15.1% (95% CI, 1.1% to 29%) At 5 yrs: 24.5% (95% CI,7.0% to 42%)	NR	**AE:** Death rate (procedure related): 0% Grade 3 AE: 4.8% Grade 1 or 2 AE: 23.8%
Ridge, 2013 [28] ABS	**OS:** (median) 48 mos , range 5 to 90 mos **OS rates** (estimated): At 1 yr: 100%, (95% CI, 100) At 3 yrs: 69% (95% CI, 42 to 85)	**DFS** (estimated): At 1 yr: 88% (95%, CI, 67-96) AT 3 yrs: 80% (CI, 58-91)	NR	**Local recurrence rate**: T1a tumours: 20% (4 of 24) T1b tumours: 63% (5 of 8)	NR	**AE:** Pneumothorax requiring chest tube: 22% (7 of 32 ablations)

<table>
<tr><th>Author, year, (ref)</th><th>Survival</th><th>Disease control (e.g., PFS, TTP, DFI)</th><th>Response / technical success</th><th>Recurrence</th><th>Risk factors, predictors, subgroups</th><th>LOS and AE</th></tr>
<tr>
<td>Lanuti, 2012 [29,87]</td>
<td>OS (median): 44.3 mos
OS rates:
At 3 yrs: 67%
At 5 yrs 31%
OS (median): 30 mos [87]
OS rates [87]:
Overall: 74%
At 2 yr: 78%
At 4 yrs: 47%</td>
<td>DFS (median): 25.5 mos [87]</td>
<td>NR</td>
<td>Recurrence: 38% (21 of 55 treatments)
In the ablated tumour bed: 33%
Regionally: (7%) and distant (4%)
Local progression: 31.5% of tumours [87]</td>
<td>Subgroups: tumour size, electrode type
<table>
<tr><th></th><th>Tumours <3 cm</th><th>Tumours ≥3 cm</th></tr>
<tr><td>Recurrence</td><td>29% (45 lesions)</td><td>80% (10 lesions)</td></tr>
<tr><td>DFS: (median)</td><td>59 mos</td><td>29 mos, P=0.03</td></tr>
<tr><td></td><td>Single electrode</td><td>Cluster electrode</td></tr>
<tr><td>Recurrence</td><td>11%</td><td>27%, P=0.004</td></tr>
</table>
</td>
<td>AE:
Pneumothorax: 18% (of ablations)
30-d mortality: 0 [87]
AE (most common) [87]:
Pneumothorax: 13%
Pneumonia: 16%
Pleural effusion: 21%</td>
</tr>
<tr>
<td>Ambrogi, 2011 [30]</td>
<td>OS (median): 33.4 mos
OS rates:
At 1 yr: 83%
At 3 yrs: 40%
At 5 yrs: 25%

CSS (median): 41.4 mos
CSS rates:
At 1 yr: 89%
At 3 yrs: 59%
At 5 yrs: 40%</td>
<td>DFI: (median) 39 mos</td>
<td>CR: 59.3% (stage Ia: 65.9%, stage Ib: 40%)
Lung function tests before and 6 mos after the procedures: NS</td>
<td>NR</td>
<td>Subgroups: Tumour stage
Stage Ia vs. stage Ib:
Complete ablation: 66% vs. 40%, P=0.01
Progression-free interval: (mean) 30.2 vs. 13.4 mos, P=0.009
DFI: data not reported, P=0.01
OS (median): 35 vs. 20 mos, P=0.02</td>
<td>AE:
Pneumothorax: 7%
Major AE: 5%</td>
</tr>
<tr>
<td>Hiraki, 2011 [31]</td>
<td>OS (median): 67 mos, (mean): 59 mos
OS rate
At 1 yr: 94%
At 2 yrs: 86%
At 3 yrs: 74%
At 4 yrs: 67%
At 5 yrs: 61%

CSS rate:
At 1 yr: 100%
At 2 yrs: 93%
At 3 yrs: 80%
At 4 yrs: 80%
At 5 yrs: 74%</td>
<td>DFS (median and mean): 42 mos
DFS rate:
At 1 yr: 82%
At 2 yrs: 64%
At 3 yrs: 53%
At 4 yrs: 46%
At 5 yrs: 46%</td>
<td>NR</td>
<td>Local progression: 31% of the tumours</td>
<td>Subgroups:
Tumour size:
Local progression rate:
Tumours ≤2 cm: 33% (10/30 tumours)
Tumours >2.1 cm and <3 cm: 40% (4/10 tumours)
Tumours ≥3 cm: 17% (2/12 tumours)
Stage IA vs. IB:
OS rates:
At 1 yr: 95% vs. 92%
At 2 yrs: 89% vs. 75%
At 3 yrs: 83% vs. 50%
At 4 yrs: 73% vs. 50%
At 5 yrs: 66% vs. 50%, P=0.057</td>
<td>AE:
Grade 2: 12% of the sessions
Grade 3: 6% of the sessions.
Grade 4 or 5: 0</td>
</tr>
<tr>
<td>Beland, 2010 [32]</td>
<td>NR</td>
<td>DFS (median):
23 mos</td>
<td>NR</td>
<td>Recurrence:
No recurrence: rate: 57%; (mean follow-up) 17 mos, range, 1 to 72 mos</td>
<td>Factors associated with recurrence:
Tumour size p=0.02;
Tumour stage: p=0.007</td>
<td>NR</td>
</tr>
</table>

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
				Recurrence: 43% of tumours, (mean follow-up) 14 mos, range, 2 to 48 mos Recurrence after ablation was: Local: 38% Intra-pulmonary: 18% Nodal: 18% Mixed: 6% Disatant metastases: 21%		
Studies of Lung Metastases						
Ferguson, 2015 [33]	**OS**[b] (median: 33.3 mos) **OS rate**: At 1 yr 89%, At 3 yrs: 44% At 5 yrs: 19.9%	**DFS rates** At 12 mos: 60.5%, At 35 mos: 14.4% At 60 mos: 7%	NR	NR	**OS rate of subgroups of patients**: CRC resection and peritonectomy (9% of pts); (median) 26 mos, CRC resection and liver resection (67% of pts): (median) 38 mos, Resection of primary CRC alone (37%): (median) 27 mos **Prognostic factors:** Lesion size, lesion number and pre-RFA CEA levels were not prognostic of OS or DFS.	**Mortality**: Death rate during follow-up: 54.8% **AE**: Pneumothorax: 107 of 199 procedures (53.8%) 18.6% of which required chest drain. Chest abscess: 1 procedure Pneumonia: 5 procedures Hemorrhage: 1 procedure Hydro-pneumothorax: 1 pt Bronchopulmonary fistula: 2 pts
Wang, 2015 [34]	**OS**[b] (median): 33 mos (95% CI: 21.6 to 44.4) **OS rates:** At 1 yr: 88.6%, At 2 yrs: 59.3% At 3 yrs: 42.8%	NR	**CR**: 88% of lesions; **PR**: 6% of lesions **PD**: 4.5% of lesions	NR	NR	**AE**: Pneumothorax: 8.6% Pneumorrhagia: 8.6% Pleural effusion: 5.7% Fever: 11.4% Thoracalgia: 11.4%
Matsui, 2015 [35]	**OS** (median): 67 mos **OS rates**: At 1 yr: 95.2% At 3 yrs: 65% At 5 yrs: 51.6%	NR	NR	**Tumour progression rate:** 14%	Prognostic factors (negative): CEA level ≥5 ng/mL (p=0.03) Presence of extrapulmonary recurrences at time of RFA (P=0.001)	**AE**: Grade 3: 1.8% of the sessions

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Gillams, 2013 [36]	**OS**: 41 mos **OS rates:** At 3 yrs: 57%	NR	NR	NR	**Subgroups** **Tumour size**: OS for pts with tumours ≤2cm: At 3 yrs 64% OS for pts with tumours 2.1 to 4 cm: At 3 yrs: 44%, P=0.08 **Number of tumours ablated**: NS	**AE:** Major: 3.9%
Petre, 2013 [37]	**OS:** Median: 46 mos (95% CI, 27.8 to 47.3) **OS rates:** At 1 yr: 95% (95% CI, 82% to 99%) At 2 yrs: 72% (95% CI, 52% to 85%) At 3 yrs: 50% (95% CI, 26% to 71%)	NR	NR	**Local tumour progression:** At 1 yr: 92% (95% CI, 82% to 97%) At 2 yrs: 77% (95% CI, 58% to 88%) At 3 yrs: 77% (95% CI, 58%-88%)	NR	NR
Hiraki, 2011b [38]	**OS rates:** At 1 yr: 87% (95% CI, 76% to 99%) At 2 yrs: 57% (95% CI, 38% to 76%) At 3 yrs: 57% (95% CI, 38% to 76%)	NR	**Technical success:** 92% at 1, 2 and 3 yrs **Repeat ablation success:** 94% at 1, 2 and 3 yrs	NR	**Prognostic factors of better survival**: Absence of intrahepatic recurrence (p<0.001) Child-Pugh class A disease (p<0.001) Absence of liver cirrhosis (p<0.001) Absence of hepatitis C virus infection (p=0.006) AFP level ≤10 ng/mL (p=0.007)	**AE**: Procedural mortality: 0 Major: 25% of the sessions (16/65) Minor: 35% of the sessions (23/65)
Von Meyenfeldt, 2011 [39]	NR	**PFS** (median estimate): 4 mos (95% CI:2.7 to 5.3) **PFS rates:** At 1 yr: 33% At 3 yrs: 11%	NR	**Local progression rate:** At 2 yrs: 35% **OS rate:** At 3 yrs: 69%	**Subgroups: Pts considered tumour-free after their first RFA vs. pts with residual disease** **OS rate at 3 yrs:** 79% vs. 49%, p=0.01	**AE:** Pneumothorax: 34% Major AE : 6% Treatment-related death: 2%
Soga, 2009 [40]	NR	NR	NR	**Local progression**: Overall: 33% of pts and 9% of tumours	**Prognostic factors:** Tumour diameter >3 cm was a prognostic factor: OR 10.0, 95% CI 0.017 to 0.581, p=0.01 **Subgroups:** **Local progression:** *Curative vs. palliative*: 8% vs. 10% of tumours, p=0.31, and 13% vs. 46% of pts, p=0.12 *Tumours ≤3 cm vs. tumours >3cm:* 7% vs. 33%, p<0.04 **OS rates:** Curative vs. palliative RFA: 100%vs. 67%, p<0.05	**AE:** Major AE: Pneumothorax 7%, aspiration pneumonia 1% Minor AE: <5%

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
					At 1 yr: 100% vs. 90% At 3 yrs 100% vs. 52% At 5 yrs: 100% vs. 52% Recurrence: 40% of the curative RFA	
Yamakado, 2009 [41]	**OS (median):** 38 mos **OS rates:** At 1 yr: 83.9% (95% CI, 75.2 to 92.7%), At 3 yrs: 56.1% (95% CI, 41.7 to 70.5%) At 5 yrs: 34.9% (95% CI, 18.0 to 51.9%)	**DFI:** 33.4±26.6 mos	NR	**Local progression rates:** At 1 yr: 10.1% (95% CI, 2.9 to 17.3%) At 3 yrs: 20.6% (95% CI, 8.9 to 22.2%) At 5 yrs: 20.6% (95% CI, 8.9 to 22.2%)	**Prognostic factors:** Absence of extrapulmonary metastases: HR 0.098;95% CI 0.040 to 0.241, p<0.0001 Normal CEA level: HR 0.098; 95% CI, 0.107 to 0.774, p<0.02 **Subgroups** **Local progression of tumours ≤3 cm vs. >3 cm**: At 1 yr: 5.1% (95% CI, 0 to 10.8%) vs. 53.1% (95% CI, 16.6 to 89.7%) At 3 yrs: 13.8% (95% CI, 2.9 to14.6%) vs. 68.8% (95% CI, 33.8 to 100%) At 5 yrs: 13.8% (95% CI, 2.9-14.6%) vs. 68.8% (95% CI, 33.8-100%)(p<0.001) **OS of tumours ≤3 cm vs. >3 cm**: At 1 yr: 86.9% (95% CI, 78.5 to 95.4%) vs. 56.3% (95% CI, 17.3 to 95.2%) At 3 yrs: 61.9% (95% CI, 47.2 to 76.6%) vs. 0% At 5 yrs: 38.5% (95% CI, 20.2 to 56.8%) vs. 0% (p<0.001). **OS of absence vs. presence of extrapulmonary metastases:** At 1 yr: 97.7% (95% CI, 93.3 to 100%) vs. 53.3% (95% CI, 31.7 to 74.9%) At 3 yrs: 82.5% (95% CI, 68.2 to 96.8%) vs. 6.0% (95% CI, 0 to -17.3%) At 5 yrs: 57.0% (95% CI, 34.7 to 79.2%) vs. 0%, p<0.0001. **OS of negative vs. positive CEA** At 1 yr: 96.9% (95% CI, 90.8-100%) vs. 73.3% (95% CI, 58.9 to 87.7%) At 3 yrs: 86.1% (95% CI, 71.1 to 100%) vs. 32.8% (95% CI, 14.3 to 51.3%) At 5 yrs: 62.5% (95% CI, 36.3 to 88.6%) vs. 11.7% (95% CI, 0 to 30.1%), p<0.0002	**AE:** Treatment-related mortality: 0 Pneumothorax requiring chest tube: 12.9% Pleural effusion requiring chest tube:1.4%

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Studies of Primary Lung Cancer and Lung Metastases, or not specified						
Akhan, 2016 [42]	**OS:** For 10 pts with NSCLC (median): 27 mos (standar error [SE], 6.5 mos). For 39 pts with malignancies: 50 mos (SE 2.7 mos) **OS rates**: For colorectal cancer metastases (16) pts), at 1 yr: 94%; at 2 yrs: 80%; at 3 yrs: 68%; and at 4 yrs: 23%.	NR	**Success rate:** Primary: 79.5% After re-treatment (10 tumours were retreated): 87.5%	Tumour progression: 21% of tumours (23 tumours) **RFS:** For 10 pts with NSCLC (median): 11 mos (SE 2.7 mos). For 39 pts with malignancies: 5 mos (SE, 5.6 mos) **RFS rates:** For 39 pts with malignancies at 1 yr: 32%; at 2 yrs: 19%; and at 3 yrs: 12%.	**Subgroups:** *Colorectal cancer metastases (16 pts)* OS (median): 50 mos (SE, 5.1 months) OS rates: At 1 yr: 94% At 2 yrs: 80% At 3 yrs: 68% At 4 yrs: 23% RFS (Median): 4 mos (SE, 1.0 months); At 1 yr: 32% At 2 yrs: 19% At 3 yrs: 12%	**AE** 24.6% (30/122 sessions) Pneumothorax: 15.6%
Kodama, 2015 [43]	**OS rate:** At 1 yr: 81.2% (95% CI: 67.6 to 94.8).	NR	NR	Tumour progression rate At 1 yr: : 12.7% (95% CI: 1 to 25.5)	NR	AE: Grade 3: 12 pts (12%) Grade 2: 13 pts (39%)
Garetto, 2014 [44]	**OS rates:** At 1 yr: 84.5% At 2 yrs: 65.4% At 3 yrs: 51.5%	**TTP**: (Mean) 19 mos	**CA** rate: 88% **Difference in diameter** of lesions achieving CA and PA: 20 vs. 38 mm, p=0.0001	**Recurrence rate:** 18.4% of CA	**Factors predictive of CA:** A threshold of 30 mm (p=0.003) Histological type: NSCLC: 75%; Metastases: 94%; p=0.0305. **Predictors of survival at 3 yrs:** Coexistence of other metastases (p=0.0422) Diameter <20 mm (p=0.0323) Local effectiveness or RFA was not a predictor.	**AE**: 31% Major AE: 7%
Alexander, 2013 [45]	NR	NR	NR	NR	**Predictors of rib fracture**: Increased age, characteristics of the tumour (i.e., size), and history of radiation therapy were not predictor. *Sex*: women's risk was 2.825 times higher than mens's (95% CI: 1.044 to 7.648, p=0.0410). *Tumour distance from chest wall:* As the tumour distance from the chest wall increased by 1 cm, the probability of fracture decreased by 36% (OR per cm: 0.36; 95% CI, 0.198 to 0.654, p=0.0009). *Ablation zone distance from chest wall*: each 1-cm increase distance decreases the probability of	**Rib fractures** near the area of ablation: 13.5% (22 of 163 pts). **Distance** between ablation zone and fractured rib: (mean) 0.49 cm, (range, 0 to 5.2 cm).

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
					fracture by 23.4%, (OR per cm: 0.234, 95% CI, 0.072 to 0.760, p=0.0159). *Ablation zones involving the visceral pleura*: OR: 4.808 (95% CI: 1.079 to 21.277), p=0.039 *Risk of fracture with RFA*: 15.9% (95% CI, 10.2 to 24) *Risk of fracture with MWA:* 2.7% (95% CI, 0.7 to 10.4), p=0.0396. *Risk of fracture with both RFA and MWA:* 25% (95% CI, 6.2 to 62.8), p<0.049.	
Galbis Caravajal, 2013 [46]	**OS** (median): 16±3.57 (rage: 8.99 to 23) **OS rate**: 32%, mean 26.61±3.17 mos (range: 20.38±32.83),	NR	NR	NR	NR	**AE:** Pneumothorax: 10 Pleural effusion: 12 Perilesional pneumonitis: 9 Other: 12
Baodong, 2011 [47] ABS	**OS (median):** 28 mos **OS rates:** At 2 yrs 57.7%	NR	NR	NR	NR	NR
Huang, 2011 [48]	**OS:** **OS rates:** At 1 yr: 68.2% At 2 yrs: 35.3% At 5 yrs: 20.1%	**PFI:** median 21.6 mos	NR	**Local progression:** 23.7% (78 pts)	**Subgroups** **Local progression by tumour size** Tumours <3 cm (n=253): 26.88% Tumours ≥3 cm and ≤4 cm (n=102): 27.45% Tumours >4 cm (n=81):41.96% <3 cm vs. ≥3 cm and ≤4 cm, X^2=0.12, p=0.912 <3 cm vs. >4 cm X^2=6.593, P=0.01 ≥3 cm and ≤4 cm vs. > 4 cm X^2=4.253, p=0.039 **Pts with NSCLC:** OS rates: At 1 yr: 80.1% At 2 yrs: 45.8% At 5 yrs: 24.3% **Pts with metastases:** At 1 yr: 50.6% At 2 yrs: 30.1% At 5 yrs: 17.3%	**AE**: 34.3% Mortality at 30 ds: 0.6% Pneumothorax: 19.1% Hemoptysis: 4.2% Hemothorax: 3% Pneumonia: 4.5% Pericardial tamponade0.9% Needle-track implantation: 1.8% at 4 to 6 mos after RFA
Kashima, 2011 [49]	NR	NR	NR	NR	**Risk factors for AE:** *Risk factors for aseptic pleural effusion:* Puncture number (p<0.02) Previous systemic chemotherapy (p<0.05) *Risk factors for pneumonia*: Previous external beam radiotherapy (p<0.001) Age (p<0.02) *Risk factor for lung abscess:*	**AE**: Mortality: 0.4% Grade 3 and 4 complication rate: 9.8%; among these: Aseptic pleuritic: 2.3% Pneumonia: 1.8%

<table>
<tr><th>Author, year, (ref)</th><th>Survival</th><th>Disease control (e.g., PFS, TTP, DFI)</th><th>Response / technical success</th><th>Recurrence</th><th>Risk factors, predictors, subgroups</th><th>LOS and AE</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Emphysema (p<0.02)
Risk factors for bleeding:
Serum platelet count (p<0.002)
Tumour size (p<0.02)
Risk factor for pneumothorax:
Emphysema (p<0.02)</td><td>Lung abscess: 1.6%
Bleeding: 1.6%
Pneumothorax: 1.6%
Bronchopleural fistula: 0.4%
Brachial nerve injury: 0.3%
Tumour seeding: 0.1%
Diaphragm injury: 0.1%</td></tr>
<tr><td>Nour-Eldin, 2011 [50]</td><td>Mortality: 0.4%</td><td>NR</td><td>NR</td><td>NR</td><td>Risk factors for hemorrhage:
Lesions of <1.5 cm diameter (P=0.007);
Basal and middle lung zone lesions (P=0.026);
Increased needle track distance traversing the lung >2.5 cm (p=0.0017);
Traversing pulmonary vessels in the track of ablation (p<0.001);
Use of multi-tined electrodes (p=0.004).</td><td>AE:
Incidence of pulmonary hemorrhage: 17.7% (44/248 sessions)
Incidence of pleural effusion: 4% (8/248 sessions)
Incidence of hemoptysis: 16.1% (40/248 sessions)</td></tr>
<tr><td>Hiraki, 2010 [51]</td><td>NR</td><td>Local control rates: 85% (213/252)
Primary lung cancer
At 6 mos: 97%
At 12 mos: 86%
At 18 mos: 81%
At 24 mos: 76% p=0.58</td><td>NR</td><td>NR</td><td>
<table>
<tr><th>Tumour type</th><th>Local control</th></tr>
<tr><td>CRC</td><td>At 6 mos: 98%
At 12 mos: 88%
At 18 mos: 86%
At 24 mos: 86%, p=0.023</td></tr>
<tr><td>Lung cancer</td><td>At 6 mos: 100%
At 12 mos: 89%
At 18 mos: 65%
At 24 mos: 0%, p=0.086</td></tr>
<tr><td>RCC</td><td>At 6 mos: 96%
At 12 mos: 86%
At 18 mos: 80%
At 24 mos: 76%, p=0.89</td></tr>
<tr><td>HCC</td><td>At 6 mos: 89%
At 12 mos: 82%
At 18 mos: 82%
At 24 mos: NR, p=0.076</td></tr>
</table>
Relative risk of local progression by tumour size:
<table>
<tr><th></th><th>1-9 mm</th><th>10-19 mm (HR (95% CI)</th><th>≥20 mm (HR (95% CI)</th></tr>
<tr><td>Primary Lung cancer</td><td>Ref</td><td>5.31 (1.45–19.5), p=0.012</td><td>16.9 (3.99–71.9), p<0.001</td></tr>
</table>
</td><td>NR</td></tr>
</table>

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
					CRC: Ref; 4.88 (1.35–17.6), p=0.016; 13.8 (3.37-56.4), p<0.001 Lung cancer: Ref; 5.01 (1.39–18.1), p=0.014; 14.3 (3.52-58.0), p<0.001 RCC: Ref; 4.92 (1.35–17.9), p=0.016; 14.7 (3.57-60.3), p<0.001 HCC: Ref; 5.26 (1.46–18.9), p=0.011; 16.7 (4.06-68.7), p<0.0001	
Chua, 2010 [52,88]	**OS (median):** 51 mos (95% CI: 19 to 83 mos) **OS rates:** At 3 yrs: 60% At 5 yrs: 45%	**PFS:** (median) 11 mos, 95% CI 9 to 14 mos	**CR:** 26% **PR:** 20% **Stable Disease:** 39% **PD**: 16%	NR	**Predictors of OS:** DFI: HR 0.4, 95% CI 0.2 to 0.8, P=0.013; Response to treatment: HR 2.5; 95% CI, 1.4 to 4.5, p=0.002 **Subgroup:** *Pts with colorectal metastases* **OS** (median): 36 mos (95% CI, 30 to 43) **OS rates:** At 1 yr: 87%; at 2 yrs:66%; at 3 yrs: 50%; at 5 yrs: 30% **Predictors of OS:** Response to RFA: HR 3.8; 95% CI, 2.2 to 6.5, p<0.001 Repeat RFA: HR 0.2; 95% CI, 0.10 to 0.6, p=0.002 Extrapulmonary metastases: HR 3.0; 95% CI, 1.34 to 6.64, p=0.008 Adjunct chemotherapy: HR 0.3; 95%, CI 0.10 to 1.03, p=0.05	**LOS:** (median) 2 ds, range1 to 16 ds **AE:** 45% (of which 30% required chest tube placement) **Predictors of AE:** 2 lesions: HR 4.6, 95% CI 1.5 to 13.6, p=0.006
Steinke, 2010 [53] **ABS**	NR	NR	NR	NR	NR	**Technical problems:** <5% **AE**: Pneumothorax 28% Intraparenchymal hemorrhage: 5% Pleural effusion: <5%
Bozzi,, 2009 [54] **ABS**	NR	NR	NR	NR	NR	**AE:** Major: 8.1% of 160 procedures Minor: 18% of 160 procedures
Zhu, 2009 [55]	Mortality rate: 0%	NR	NR	NR	**Risk factors for AE:** *Overall morbidity:* >2 lesions ablated OR 15.812; 95% CI, 0.352 to 71.001, p<0.001 Length of probe trajectory OR 2.895; 95% CI, 1.105 to 7.584, p=0.03 *Hemoptysis* Hilar location of tumour: OR 59.372; 95% CI1, 214 to 129.82, p=0.040	**LOS**:1±2 ds **AE:** Morbidity rate: 43% (55 of 129) Pneumothorax:32% (41 of 129) Pleuritic pain: 18% (23 of 129)

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success	Recurrence	Risk factors, predictors, subgroups	LOS and AE
					Pneumothorax Number of lesions ablated: OR 31.614; 95% CI, 6.301 to 158.622, p<0.001 Length of probe trajectory: OR 3.108; 95% CI, 1.043 to 9.255, p=0.042. *Chest drain placement* >2 lesions ablated, OR 61.484; 95% CI, 7.038 to 197.12, p<0.001	Hemoptysis: 7% (9 of 129) Pleural effusions: 12% (15 of 129) Chest drain insertion: 20% (26 of 129)

[a] Not attributable to RFA.
[b] Calculated from the first RFA treatment.
[c] Peripheral lesions close to or involving the pleura were usually treated with RFA; larger lesions, or in cases of recurrence near a heat sink were usually treated with MWA.
[d] This study included 32 pts with stage I lung cancer, 23 cases of pts with metastases, and 4 pts other stages of lung cancer.
[e] The number of pts with early stage is not reported.

Abbreviations: ABS = abstract; AE = adverse events; AFP = alpha fetoprotein; CA = complete ablation; CEA = carcino embrionic antigen; CI = confidence interval; CR = complete response; CRC = colorectal cancer; CSS = cancer-specific survival; DFI = disease-free interval; DFS = disease-free survival; D_{LCO} = diffusing capacity of lung for carbon monoxide; ds = days; FEV1 = forced expiratory volume in the first second of expiration; HCC = hepatocellular carcinoma; HR = hazard ratio; LOS = length of hospital stay; mos = months; MWA = microwave ablation; NR = not reported; NS = not significant; NSCLC = non small cell lung cancer; OR = odds ratio; OS = overall survival; PA = partial ablation; PD = progressive disease; PFI = progression-free interval; PFS = progression-free survival; PR = partial response; pts = patients; QOL = quality of life; RCC = renal cell carcinoma; RFA = radiofrequency ablation; RFS = recurrence-free survival; SE = standard error; TTP = time-to-progression; yrs = years

Table 2a. Primary studies of cryoablation*: General characteristics.

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention(s)	Outcomes
Studies of Primary Lung Cancer				
Moore, 2015 [56] **Country**: US **Funding:** NR	Retrospective case series **Data collection**: 2006 to 2011 **Follow-up:** (mean) 51±10 mos	N = 45 Pts with stage I NSCLC (n=17), adenocarcinoma (n=21), and squamous cell carcinoma (n=9), medically inoperable with 47 T1N0M0. **Lesion size**: 1.9cm ± 0.5 (0.5–3.0 cm) **Sex:** Men 76% **Age:** (median) 74.8 yrs (range 49–85)	Cryoablation with curative intent (45 sessions). **Device:** The Endocare Per Cryo system, (Health Tronics, Inc, Austin, TX, US) with a 13 or 16 gauge cryoprobe. **Target temperature:** NR **Procedure:** 16-gauge and/or 13-gauge cyroprobes used for freeze/thaw cycle. Number and orientation of cryoablation probes based on size and shape of tumours. **Operator experience**: Performed by interventional radiologist.	OS CSS PFS Recurrence Major AE
Gao, 2014 [57] **Country**: China **Funding:** NR	Survey **Data collection:** 2005 to 2013 **Follow-up: (**range) 8 to 70 mos	N = 37 pts with stage Ib-IIIa lung cancer (this is a subset of the total sample that included also 82 pts with advanced cancer) **Lesion size:** NR **Sex:** Men 65% **Age:** NR	Percutaneous cryoablation plus traditional Chinese medicine performed with curative intent (number of sessions NR). **Device:** NR **Target temperature:** NR **Procedure:** Percutaneous cryoablation with TCM **Operator experience**: NR	OS
Studies of Lung Metastases				
Eaton, 2015 [58] **Country**: UK **Funding:** NR	Retrospective case series **Data collection**: 1995 to 2012 **Follow-up**: NR	N = 35 pts with endobronchial metastases. **Lesion size**: NR **Sex:** Men 66% **Age:** median 72 yrs (range 22-80)	Endoluminal cryoablation performed for palliation (number of session NR). **Device:** Adult-size 9 rigid bronchoscope and a straight rigid (Spembly) or flexible (Erbe) cryotherapy probe. **Target temperature:** -70˚C (Nitric oxide) **Procedure:** All pts received general anesthesia. Probe was introduced on or into tumour mass. Once uniform ice ball formed between probe tip and tumour, freezing maintained for 240 seconds before thawing. Freezing-thawing cycle repeated for 240 more seconds. Any devitalized /necrotic tissue was removed and then repeated freeze-thaw cycles in order to restore airway patency. **Operator experience**: NR	OS
de Baère, 2015 [59] ECLIPSE **Country**: France and US **Funding:** Galil Medical	Single arm prospective phase I study (per protocol analysis) **Data collection**: Jan 2012 to Mar 2013 **Follow-up**: 12 mos	N = 40 pts with lung metastases **Lesion size:** 1.4 ± 0.7 cm (range 0.3-3.4) **Sex:** Men 60% **Age:** 62.6 ± 13.3 yrs (range 26-83)	Cryoablation (48 sessions) with curative intent. **Device:** 1.5 / 2.4 mm (gauge 17 and 13) cryoablation needles (Galil Medical, Inc. [Arden Hills, MN, US]) **Target temperature:** NR **Procedure:** Three-cycle freeze-thaw phase protocol was applied with target times of 3 min freeze, 3 min thaw, 8 min freeze, 5 min stick, 8 min freeze and active thawing. A margin ≥5 mm around the tumour. **Operator experience**: NR	Local tumour control QOL OS AE

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention(s)	Outcomes
Xiao, 2011 [60] **ABS** **Country:** China **Funding:** NR	Case series **Data collection:** NR **Follow-up**: 24 mos	N = 40 pts with peripheral NSCLC. **Lesion size:** <5 cm **Sex**: NR **Age**: NR	Cryoablation (intent and number of sessions: NR) **Device:** NR **Target temperature:** NR **Procedure:** CT-guided and monitored percutaneous conformal cryoablation. Treatment with double-needle clamping cryoablation for tumours <3 cm diameter and multiple-needle conformal cryoablation for tumours 3-5 cm. **Operator experience**: NR	CR PR AE
Studies of Primary Lung Cancer and Lung Metastases				
Littrup, 2014 [61] **ABS** **Country**: US **Funding:** NR	Case series from a prospective (41 pts, 51 procedures, and 65 tumours) and a retrospective cohort (91 pts, 126 ablations, and 238 tumours) **Data collection**: NR **Follow-up**: NR	N = 132 pts 177 procedures on 303 tumours (120 primary, 183 metastatic tumours) **Lesion size:** median 2.2 cm **Sex:** NR **Age:** NR	Cryoablation (177 procedures; intent of procedure NR) **Device:** Min 2 cryoprobes per pt. **Target temperature:** NR **Procedure:** CT and/or CT-US fluoroscopic-guided percutaneous cryoablation used with min 2 cryoprobes; probe number based on formula of tumour diameter plus one. **Operator experience**: NR	Major AE Recurrence Progression
Zhikai, 2013 [62] **Country**: China **Funding:** Cancer Research Fund of Fuda Cancer Hospital, Guangzhou, China.	Case series (prospective) **Data collection:** Oct 2010 to Oct 2012 **Follow-up**: NR	N = 47 pts with central type lung cancer (22 endotracheal, 26 tracheal wall, and 21 extratracheal tumours; 32 medium or well differentiated 27 poorly differentiated tumours). **Lesion size:** <5 cm **Sex:** NR **Age:** (mean) 57 yrs, range 31 to 82 yrs.	Combined percutaneous cryoablation and endobronchial cryoablation and airway stenting: 69 sessions with treatment intent. **Device:** Percutaneous cryosurgery: An argon gas based cryosurgical unit with a single, 1.7 mm, cryoprobe (Endocare, Irvine, CA, US) was used. Endobronchial cryosurgery: 2.4mm flexible bronchoscope with a Joule-Thomson type probe (Spembly Medical, Andover, UK). **Target temperature:** Reaching -180°C at probe tip for percutaneous cryosurgery. Reaching -70°C at tip of probe for endobronchial cryosurgery. **Procedure:** *Percutaneous cryosurgery:* Two freeze/thaw cycles (argon) each cycle. Max freezing time 15 min with time varying on the visibility of an ice ball on CT and thawing was 5 min. *Endobronchial cryosurgery:* Endobronchial cryosurgery performed to treat endobronchial part first, followed by percutaneous cryosurgery. Tumour frozen (nitrous oxide) for 3 min until covered by ice ball completely and smaller tumours pulled out immediately using probe. **Operator experience**: NR	PFS
Yashiro, 2013 [63]	Case series (prospective)	N =71 pts 210 tumours (11 NSCLC and 199 metastatic tumours)	Cryoablation. Some pts also underwent systemic chemotherapy after cryoablation. 102 sessions with curative intent. **Device:** Cryoprobes from Cryocare cryosurgical unit (Endocare Irvine, CA, US). **Target temperature:**	Progression free rate Technical success*

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention(s)	Outcomes
Country: Japan **Funding:** NR	**Data collection:** Oct 2002 to Jun 2007 **Follow-up**: 3 yrs	**Lesion size:** (mean) 12.8 mm (range 3-42 mm) **Sex**: Men 61% **Age**: (mean) 58.8 yrs, range 20–82	**Procedure:** Number and size of cryoprobes used were dependent on tumour size with a max of 4 cryoprobes per lesion. Triple freeze/thaw protocol used with high-pressure argon gas for freezing. Before July 2006, freezing was 5 min for the first and second freezes and 10 min for the third freeze. After July 2006, freezing was 5 min for the first freeze and 10 min for second and third freeze. Thawing was performed with high-pressure helium gas until temperature of thermocouple in cryoprobe was 20°C. **Operator experience**: Performed by 2 authors with experience in percutaneous lung biopsy.	Risk factors for technical failure*
Niu, 2012 [64] **ABS** **Country**: China **Funding:** NR	Case series **Data collection:** Jan 2002 to Apr 2006 **Follow-up**:24 mos	N = 46 pts with stage I **Lesion size:** <5 cm **Sex**: Men 70% **Age**: (median) 64 yrs, range 12 to 95	Cryoablation with palliative intent. **Device:** Cryocare Surgical System (CRYO-20 type) with a 1.7 mm and 2.0 mm probe. **Target temperature:** Freezing at -140°C (argon) and thawing at 15°C (helium). **Procedure:** 2 to 8 cryoprobes used dependent on size, shape and location of lesion. 3 freeze-thaw cycles performed with 15 min of freezing and 5 min of thawing **Operator experience**:NR	Survival
Lin, 2012 [65] **ABS** **Country:** US **Funding:** NR	Case series **Data collection:** May 2005 to Sept 2010 **Follow-up**: NR	N = 54 pts with 80 tumours either primary lung cancer, or metastases. **Lesion size:** 2.0 cm (range, 0.5-5.5 cm) **Sex**: Men: 57% **Age**: (mean) 68.1 yrs (range, 8-90 yrs).	Percutaneous cryoablation. Number of sessions NR. **Device:** 1.7 mm and 2.4 mm probe **Target temperature:** NR **Procedure:** Ablation performed using average 2.2 cryoprobes (range 1-5) for an average of 2.1 freeze/thaw cycles (range 2-4). **Operator experience**: NR	Local tumour recurrence
Inoue, 2012 [66] **Country:** Japan **Funding:** NR	Case series **Data collection:** Oct 2002 to Dec 2008 **Follow-up**: (mean 899 ds ±778; range, 13–2,927 ds).	N = 117 pts with metastatic (104) and primary lung tumours (13) **Lesion size:** Mean ± SD: 14.0 ±8.0 mm, range: 3-65 **Sex**: Men 66.7% **Age**: (Mean ±SD) 59±15.7 yrs	Cryoablation with curative intent. 193 sessions for 396 tumours. **Device:** CRYO care cryosurgical unit (Endo-Care, Irvine, CA, US) with 2.4 mm and 3.0 mm diameter cryoprobes; 3-slice CT fluoroscopic guidance (Aquilion 64; Toshiba); Coaxial system (Daimon coaxial system; Silux) **Target temperature:** NR **Procedure:** Triple freeze/thaw cycle used with high-pressure argon gas for freezing and high-pressure helium gas for thawing. Before July 2006, freezing for first two cycles was 5 min and third cycle was 10 min. After July 2006, freezing for first cycle was 5 min and last two cycles was 10 min. The margin was ≥5mm around the tumour. **Operator experience**: Operators have previous percutaneous lung biopsy experience	AE Potential risk factors for AE

*All studies were noncomparative.
[a] Local and regional combined recurrence rate.
[b] Including pulmonary hemorrhage and pneumothorax.
Abbreviations: ABS = abstract; AE = adverse events; CR = complete response; CSS = cancer specific survival; CT = computed tomography; ds = days; mos = months; N = sample size; NR = not reported; NSCLC = non small cell lung cancer; OS = overall survival; PFS = progression-free survival; PR = partial response; pts = patients; QOL = quality of life; SD = standard deviation; TCM = traditional Chinese medicine; yrs = years

Table 2b. Primary studies of cryoablation: Summary results.

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success/ QOL	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Studies of Primary Lung Cancer						
Moore, 2015 [56]	**OS rates:** At 5 yrs: 67.8% ± 15.3 **CSS rate**: At 5 yrs: 56.6% ± 16.5	**PFS rate**: At 5 yrs: 87.9% ± 9	NR	**Recurrence rate** [a]: 36.2%	NR	Major AE: 6.4% Deaths within 30 ds of treatment: 0
Gao, 2014 [57]	**OS (median mos):** From diagnosis: 20 (95% CI 10.72–29.28) mos; From Cryoablation: 10 (95% CI 3.83–16.17) mos.	NR	NR	NR	**Subgroups:** **OS after ablation:** *Stages IIIb-IV vs. Stages Ib-IIIa:* 10 mos (95% CI, 7.35 to 12.65) vs. 10 mos (95% CI, 3.83 to 16.17); p=0.95 *Pathology type:* NSCLC vs. SCLC 10 mos (7.47 to 12.53) vs. 10 mos (7.37 to 12.63; p=0.84 *Anti-cancer therapy history:* Cryo-TCM-Only vs.Chemo-Cryo-TCM: 10 mos (95% CI, 4.99 to 15.02) vs. 8 (95% CI, 4.22 to 11.78), p=0.03. Cryo-TCM-Only vs.RT-Cryo-TCM: 10 mos (95% CI, 4.99 to 15.02) vs. 8 mos (95% CI, 2.46 to 13.54), p=0.09. Cryo-TCM-Only vs. Targeted drug-Cryo-TCM: 10 mos (95% CI, 4.99 to 15.02) vs. 10 mos (95% CI, 1.95 to 18.05), p=0.29.	NR
Studies of Lung Metastases						
Eaton, 2015 [58]	OS (median) = 34 wks OS rate at 1 yr: 37.5%	NR	NR	NR	NR	NR
de Baère, 2015 [59]	OS rate: At 1 yr: 97.5%	NR	Tumour control rate: at 6 months: 96.6%, and at 1 yr: 94.2% **QOL:** no change at 1 yr	NR	NR	Pneumothorax: 18.8% Grade 3 procedural AE: 6%
Xiao, 2011 [60] **ABS**	NR	NR	At 24 mos: CR: 86.5% (32 pts) PR: 13.5% (5 pts)	NR	NR	AE: Hemoptysis: 52.5% (21 pts) Pneumothorax: 22.5% (9 pts)

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Response / technical success/ QOL	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Studies of Primary Lung Cancer and Lung Metastases						
Littrup, 2014 [61] **ABS**	NR	NR	NR	Recurrence rate: 6.9% (21/303). Satellite recurrence: 4.3% (13/303). Progression: 2.6% (8/303)	**Subgroups:** AE: For tumours ≤3 cm 1.5% (2/134) For tumours >3cm 11.8% (9/76) (p<0.005)	Major AE rates: 6.2% (11/177).
Zhikai, 2013 [62]	NR	PFS: 11 ± 7 mos (95% CI, 9 to 13 mos)	**Technical success**: 100%	NR	**Subgroups** *PFS:* Endotracheal (22 pts) vs.tracheal wall tumours (26 pts): 8 ± 4 mos vs. 13 ± 6 mos, p < 0.05. Endotracheal (22 pts) vs. extratracheal (21 pts) tumours: 14 ± 8 mos p<0.01 NSCLC vs.SCLC: 11 ± 5 mos vs. 4 ± 2 mos, p<0.0001. Adenocarcinoma (33 pts) vs. squamous cell carcinoma (26 pts): 12 ± 9 mos vs.11 ± 6 mos, p=0.7217. Medium or well differentiated (32 pts) vs. poorly differentiated tumours (27 pts): 15 ± 8 mos vs. 7 ± 3 mos, p<0.0001.	NR
Yashiro, 2013 [63]	NR	PFS rates: At 1 yr: 80.4% At 2 yrs: 69.0% At 3 yrs: 67.7%	NR	NR	NR	NR
Niu, 2012 [64] **ABS**	**Survival rates:** At 1 yr: 100% At 2 yrs: 100%	NR	NR	NR	NR	NR
Lin, 2012 [65]	NR	NR	NR	Local tumour recurrence: 20% per tumour (16/80 tumours) and 28% per pt (15/54 pts)	NR	NR
Inoue, 2012 [66]	NR	NR	NR	NR	Risk factors for pneumothorax: *Number of cryoprobes:* OR: 12.07 (95% CI, 0.413 to 0.781), p=0.001	**AE:** Pneumothorax: 61.7% (119/193). Delayed and recurrent pneumothorax: 7.8% (15/193). Pleural effusion: 70.5% (136/193) Hemoptysis: 36.8% (71/193)

[a] Local and regional combined recurrence rate.

[b] Including pulmonary hemorrhage and pneumothorax.
Abbreviations: ABS = abstract; AE = adverse events; Chemo = chemotherapy; CI = confidence interval; CR = complete response; Cryo = cryoablation; CSS = cancer specific survival; ds = days; mos = months; NR = not reported; NSCLC = non small cell lung cancer; OS = overall survival; OR = odds ratio; PFS = progression-free survival; PR = partial response; pts = patients; QOL = quality of life; RT = radiotherapy; SCLC = small-cell lung cancer; TCM = traditional Chinese medicine; wks = weeks; yrs = years

Table 3a. Primary studies of microwave ablation*: General characteristics

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
Studies of Primary Lung Cancer				
March, 2014 [81] **ABS** **Country:** US **Funding:** NR	Case series (retrospective) **Data collection:** NR **Follow-up**: NR	N=108 pts with a single lung malignancy **Lesion size:** NR **Gender**: Men 61% **Age**: (mean) 73 yrs	Percutaneous MWA **Device:** NR **Target temperature:** NR **Procedure:** CT guided percutaneous microwave ablation for single lung malignancy. **Operator experience**: NR	TTR CSS Technical success AE
Yang, 2014 [76] **Country:** China **Funding:** NR	Case series (retrospective) **Data collection:** Feb 2008 to Oct 2012 **Follow-up**: 30 mos (range, 7 to 70 mos)	N = 47 pts with unresectable stage IA and IB (T1-2N0M0) NSCLC **Lesion size:** 51.1% >3.5 cm (range, 3.6 to 5.0); 48.9% ≤3.5 cm (range, 2.4 to 3.5) **Gender**: Men 63.8% **Age**: 69.4 yrs, range 56 to 82 yrs	MWA (47 sessions) **Device:** MTC-3C microwave ablation system (Nanjing Qi Ya Research Institute of Microwave Electric, China.) with a 100-180 mm and 14G-20G microwave antennae **Target temperature:** NR **Procedure:** Pts received local anesthesia and preemptive analgesia. Single antennae used for tumours ≤ 3.5 cm (19 tumours) and double antennae used for tumours 3.6-5.0 cm (28 tumours). The antennae were positioned into the deepest margin of lesion and the power of ablation was set to 60-80 W for 6-8 min. **Operator experience**: NR	TTR Local control CSS OS Pneumothorax AE
Studies of Primary Lung Cancer and Lung Metastases				
Splatt, 2015 [77] **Country:** Australia **Funding:** NR	Case series (retrospective) **Data collection:** May 2010 to Sept 2014 **Follow-up**: NR	51 pts with primary (62.9%) or secondary (37.1%) lung cancer T2bN0M0 **Lesion size:** (median) 24.4 mm, range 7 to 63 mm **Gender**: Men 64.7% **Age**: (mean) 71.2 yrs, range 46 to 88	MWA (70 ablations) **Device:** For the first 6 months in 2010 (8/70 cases) a lower energy system (EvidentTM system, Covidien,Boulder, Colorado, US); From late 2010 (62/70 cases), the higher powered Acculis Microwave Tissue Ablation system (AngioDynamics, Latham, New York, US) with 13G Antennae and 2 or 3.7 cm active tip **Target temperature:** Power applied ranged from 80 W to 120 W **Procedure:** pMTA inserted into target lesion and antenna position confirmed using multiplanar reformats. Ablation paramters chosen dependent on lesion size, shape and proximity to vital structures. Ablation time ranged from 2.5-15 min. **Operator experience**: NR	AE LOS
Zheng, 2014 [78] **Country:** China **Funding:** NR	Case series (retrospective) **Data collection:** Jan 2011 to May 2013	N=184 pts with 253 tumours of the lung (72.5% primary and 27.5% metastases) **Lesion size:** 3.29±1.93 cm **Gender**:	MWA (204 ablations) **Device:** The MWA therapeutic instrument (MTC-3C, Nanjing Qinghai Research Institute of Microwave Electric, China) With a 100-180 mm and a 14G microwave antennae **Target temperature:** Power of 60-80 W applied for 4-8 min	AE incidence and risk factors

Author, year, (ref), Study name Country, Funding	Design, Data collection Follow-up	Population	Intervention	Outcomes
	Follow-up: NR	Men 64.7% **Age**: 61.5±13.4 yrs, range 19 to 85 yrs	**Procedure:** Single antennae used for tumours ≤ 3.0 cm and double antennae used for tumours > 3.0 cm. Under CT fluoroscopy, microwave antennae placed into tumour and ablation performed. Antennae placed sequentially at 1 to 8 different sites dependent on shape and size of tumour. **Operator experience**: NR	
Vogl, 2013 [79] **Country:** Germany and Egypt **Funding:** NR	Case series (retrospective) **Data collection:** Jan 2009 to Jan 2011 **Follow-up**: (mean) 10.2±6.2 mos, range 6.0 to 29.2 mos	N=57 pts with 91 primary (2.2%) or secondary tumours **Lesion size:** <3 cm **Gender**: Men 47.4% **Age**: (mean) 57.5±12.2 (SD), range 24.9 to 80.7 yrs	Percutaneous MWA (91 sessions) **Device:** Microwave ablation system (Covidien) 12, 17 or 22 cm microwave antennae **Target temperature:** The output power ranged from 25 to 45 W (mean, 42.7 W). **Procedure:** Mean ablation time was 17.7 min (range: 5-30 min). Procedure stopped when index tumour was completely covered by the ablation zone. **Operator experience**: 2 interventional radiologists with more than 8 and 15 years of experience in interventional oncologic radiology	Technical success Local progression TTP Risk factors predictive of local control

*All studies were noncomparative.
[a] Post-ablation syndrome: fever, fatigue, general malaise and vomiting

Abbreviations: ABS = abstract; AE = adverse events; CSS = cancer-specific survival; CT = computed tomography; LOS = length of hospital stay; mos = months; MWA = microwave ablation; NA not applicable; OS = overall survival; N = sample size; NR = not reported; NSCLC = nonsmall cell lung cancer; pMTA = percutaneous microwave tissue ablation; pts = partients; TTP = time to progression; TTR = time to recurrence; yrs = years

Table 3b . Primary studies of microwave ablation: Summary results.

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Studies of Primary Lung Cancer					
March, 2014 [81] **ABS**	**CSS**: 42 mos, 95% CI, 38 to NA	**TTR (median):** 62 mos 95% CI: 29 to NA	**Recurrence rates** (estimated): At 1 yr: 22% At 2 yrs: 36% At 3 yrs: 44%	**Subgroups:** *Tumours <3 cm vs. >3 cm* **Technical success**: OR 11.1: 95% CI, 2.97 to 41.1 p=0.0003 **AE:** OR 0.5, p=0.09 **Recurrence rates** (estimated): At 13 mos: 17% vs. 31% For every mm increase in the original tumour diameter: The odds of not attaining success increased by 7%, 95% CI: 3% to 10%, p=0.0002 The odds of one or more AE increased by 3%, 95% CI: 1% to 5%, p=0.04	**AE:** ≥1 complication: 54% of patients: Pneumothorax: 32%; bronchopleural fistula: 2%; hospital admission: 28%; pain 20%; infection 7%; postablation syndrome 4% and ARDS 4%
Yang, 2014 [76]	**OS** (median): 33.8 mos, 95% CI: 31.9 to 35.7 mos **OS rates:** At 1 yr: 89% At 2 yrs: 63% At 3 yrs: 43% At 5 yrs: 16% **CSS** (median): 47.4 mos, 95% CI: 25.7 to 69.1 mos	**TTR**: (median) 45.5 mos, 95% CI: 28.8 to 61.8 mos	**Local progression rate:** 27.7% of the sessions **Local control rate:** At 1 yr: 96% At 3 yrs: 64% At 5 yrs: 48%	**Subgroups** OS for tumours ≤3.5 cm At 1 yr: 91% At 2 yrs: 72% At 3 yrs: 59% At 5 yrs: 36% Tumours ≤3.5 cm were associated with better survival than tumours >3.5 cm (p=0.016)	**AE:** Pain: severe in 6% Post-ablation syndrome[a]: 32% Pneumothorax: 63.8% (13.5% requiring chest tube) Hemoptysis: 31.9% Pleural effusion: 34% Pneumonia: 14.9% Bronchopleural fistula: 2.1%
Studies of Primary Lung Cancer and Lung Metastases					
Splatt, 2015 [77]	NR	NR	NR	NR	**LOS:** (mean) 1.62 ds **AE:** 20% of ablations Mortality: 1.4% (within 30 ds of the procedure) Pneumothorax requiring chest tube: 12.9% Pleural effusion requiring chest tube: 5.7% Pulmonary hemorrhage: 2.9% Infections: 2.9% Mechanical failure: 1.4% Chest wall burn 1.4% Pleural seeding: 1.4%

Author, year, (ref)	Survival	Disease control (e.g., PFS, TTP, DFI)	Recurrence	Risk factors, predictors, subgroups	LOS and AE
Zheng, 2014 [78]	NR	NR	NR	**Risk factors for** Pneumothorax: emphysema (p=0.001) Pleural effusion: distance of <1 cm from chest wall to target tumour (p=0.014) Pneumonia: tumour maximal diameter (p=0.04); number of pleural punctures (p=0.001), and ablation time (p=0.006)	**Major AE:** 20.6% of sessions including: Pneumothorax: 15.7% Pleural effusion: 2.9% Pneumonia: 2.9% Pulmonary abscess: 0.5% Death (procedure-related): 0.5%
Vogl, 2013 [79]	NR	**TTP** (mean): 8.3±5.5 mos, range 2.1 to 25.2 mos; (median) 22.6±12.4 mos	**Local progression** (median) 22.6±12.4 mos **Local progression rates:** 36.8% of pts and 33% of tumours	**Risk factors** *For local progression:* Irregular shape of tumour, p=0.03 J/mm^3 applied to the tumour, p=0.001	**Repeated ablation:** 7.7% of tumours

[a] Post-ablation syndrome: fever, fatigue, general malaise and vomiting

Abbreviations: ABS = abstract; AE = adverse events; ARDS = acute respiratory distress syndrome; CI = confidence interval; CSS = cancer specific survival; ds = days; LOS = length of hospital stay; mos = months; MWA = microwave ablation; NA = not applicable; NR = not reported; OR = odds ratio; OS = overall survival; TTP = time to progression; TTR = time to recurrence; yrs = years

Table 4. Abstracts of interim analyses.

Study	Intervention(s)	Design	Population	Interim Results
Fanucchi, 2014 [85]	Wedge resection and RFA	Observational comparative (retrospective)	41 early stage NSCLC in high-risk pts	Mortality: 0 vs. 0 Morbidity: 31.7% vs. 9.3%, (p=0.011) Local recurrence: 12% vs. 33% (p=0.026) OS rates: At 1 yr 94% vs. 100% At 3 yrs 54% vs. 67% CSS rates: At 1 yr 100% vs. 100% At 3 yrs 67% vs. 94%, p = NS
Catena, 2012 [84]	RFA or MWA	Case series	52 pts with 62 tumours with primary lung cancer or metastatic disease	Local recurrences: 2 Technical success: 100% AE: Pneumothorax: 13 procedures LOS: 2 ds
Zhang, 2011 [83]	RFA	Case series	226 pts with 250 NSCLC or metastases	1.6% of lesions showed complete necrosis, 70.4% showed PR, 7.6% showed progressive disease and received second session of RFA. Procedural mortality 0% Pneumothorax in 26 pts, 4 requiring drainage, Intrapulmonary hemorrhage in 4 pts, Chest pain in 14 pts, Cough in 10 pts.
Fanucchi, 2010 [82]	Wedge resection and RFA	Observational comparative (retrospective) 32 pts received wedge resection and 34 RFA	Pts with early stage NSCLC	Mortality 0% Morbidity rates: 31.5% vs. 26.5% No statistically significant difference in survival rates at a mean follow-up of 29.9 months for wedge resections and 31.6 months for RFA Disease free rates: 78% vs. 56%. Local recurrence rate 6.2% vs. 41.1% (p=0.002)
Yamauchi, 2013 [86]	Cryotherapy	Case series	22 pts with 34 stage I NSCLC	Pneumothorax: 28%, Pleural effusion: 31%. Local tumour progression: 3%. Local disease progression-free interval: 88±8 mos (mean). Local disease progression-free interval (median): not achieved. OS rates: at 3 yrs: 90.7%. OS (mean): 88±8 mos; median not achieved. CSS: 100%.

Abbreviations: AE = adverse events; CSS = cancer specific survival; ds = days; LOS = length of hospital stay; mos = months; MWA = microwave ablation; NS = not significant; NSCLC = nonsmall cell lung cancer; OS = overall survival; PR = partial response; pts = patients; RFA = radiofrequency ablation; yr = year